MASTER'S THESIS

Enteral Nutrition in Critically Ill Patients: The ENCIP Study

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Award date:
2017

FACULTY OF HEALTH SCIENCES AND MEDICINE

Research Dissertation

ENTERAL NUTRITION IN CRITICALLY ILL PATIENTS: The ENCIP Study

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Submitted to Bond University
in partial fulfilment of the requirements for the degree of
Master of Nutrition and Dietetic Practice

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Introduction

Nutrition in critical illness plays a pivotal role in ICU [1,2]. The importance of adequate nutrition among critically ill patients in amplified by an increase in the metabolic stress response, impaired immune function and the severity of illness [3]. As a result, the delivery of nutrition in this context is often difficult, which leads to a cumulative energy and protein deficit, causing muscle wastage [3]. In turn heighten the risk of malnutrition, resulting in higher incidences of complications and poorer outcomes including increased ICU length of stay, infectious complications and increased morbidity and mortality [4,5].

Nutrition support, often referred to as the provision of calories, protein, minerals, vitamins and other vital micronutrients, plays a fundamental role in the ICU [5]. Common modes of delivering nutrition support include enteral and parenteral nutrition [6]. While both enteral and parenteral nutrition play an important role in ICU, the best practice guidelines recommend the use of enteral nutrition and early initiation to reduce the risk of patient outcomes [1,6-9]. Despite enteral nutrition identified as an integral component of care in ICU, the current literature highlights a high prevalence of underfeeding in ICU worldwide [4].

This dissertation explores the current body of evidence for the nutritional management in critical illness in a literature review followed by an original research manuscript of a prospective observational study conducted from October 2016 to February 2017. The study aimed to assess the nutritional adequacy of enteral nutrition (EN) fed critically ill patients. Additional outputs from this dissertation include an abstract submitted to the 2017 Dietitians Association Australia Conference.

Literature Review

Nutrition issues in Critical Care

Providing nutrition support has been widely recognised as an integral part of care for critically ill patients[6,7,9]. The importance for adequate nutrition among critically ill patients is amplified by an increase in the metabolic stress response, impaired immune function and the severity of illness[1,8]. It is often difficult to deliver nutrition in this population with increased requirements in the context of altered metabolic and immune response, which lead to a cumulative energy and protein deficit resulting in muscle wastage[1,7]. Subsequently, critically ill patients are at an increased risk of malnutrition which in turn has been associated with longer length of stay in ICU, poorer clinical and functional outcomes, increased morbidity and mortality[6-11].

Malnutrition

Malnutrition is of high prevalence in the hospital inpatient setting with 20-50% of adults being considered malnourished in acute care[12-14]. Malnutrition is defined as the deficiency or excess of energy, protein and nutrients to meet the metabolic requirements[15]. The associated consequences for malnutrition include an increased length of stay (LOS), reduced quality of life and increased risk of morbidity and mortality[5,14]. Validated malnutrition screening tools are a feasible method of identifying if a patient is at risk of malnutrition and assess whether further nutrition intervention is required[14]. Guidelines suggest malnutrition in the acute setting should be identified using validated malnutrition screening tools (such as the Malnutrition Screening Tool (MST), Mini Nutrition Assessment (MNA), Malnutrition Universal Screening Tool (MUST), Nutrition Risk Screening (NRS-2002) and Simplified Nutrition Assessment Questionnaire (SNAQ(c)) (Level II-III evidence)[14] which include

evaluation of weight loss, appetite, muscle and subcutaneous fat loss and nutrition-impact symptoms (nausea, vomiting, diarrhoea).

However, there is no consensus of a malnutrition screening tool that has been validated in patients within the ICU[6]. The challenge in identifying and assessing malnutrition in critical illness is due to the likelihood of the patient being ventilated and therefore unable to provide historical data[6]. Objective measures such as inflammatory markers (C-reactive protein, interleukin-6 and serum albumin) are unreliable reflections of nutritional status, as they are influenced by other factors. In addition to this anthropometric measures are challenging to measure and difficult to interpret as it may be masked by fluid retention[7,8,10]. The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines for ICU suggest using the Nutrition Risk Screening (NRS) or the Nutrition Risk in Critically ill (NUTRIC) score, which are assessment tools that include the assessment of disease severity to identify malnutrition risk in ICU patients[6].

A recent systematic review including the review of 20 prospective cohort studies examined the association of malnutrition and the clinical outcomes of critically ill patients[5]. The studies included in the analysis used either the Subjective Global Assessment (SGA) or Mini Nutrition Assessment tool, or the Nutrition Risk Screening (NRS) or Malnutrition Universal Screening Tool (MUST) to assess malnutrition risk. There was large variability in the prevalence of malnutrition for a heterogeneous ICU population (37.8% – 78.1%), however higher than general wards[16,17]. Trials that studied specific groups such as liver transplantation and acute kidney injury had higher rates of malnutrition prevalence (52.6% and 82.0% respectively). When investigating the association of malnutrition and mortality, malnutrition detected using the SGA was associated with higher hospital mortality and longer ICU LOS.

Malnutrition identified by NRS and MNA-SF were associated with hospital mortality. While the MUST found an association with malnutrition and 1-year mortality. There was an independent positive association between malnutrition and the incidence of infections, risk of ICU readmission and percentage of elderly patients being discharged to nursing facilities. Despite the variability in methods for assessing and screening malnutrition, this study highlighted the high prevalence of malnutrition and the impact it has on clinical outcomes. The study also highlights the importance of using tools to assess or screen for malnutrition to determine an appropriate tailored intervention.

Determining energy and protein requirements

The suggested methods of determining energy requirements by the current guidelines include the use of indirect calorimetry (IC) or weight-based equations[7,8,10]. Indirect calorimetry (IC) is the gold standard to accurately determine resting energy expenditure (REE). However, the use of IC in ICU may be impacted by clinical variables and the availability of IC[18,19]. The tight calorie control study (TICACOS) by Singer et al.[20], was able confirm the efficient delivery of energy and protein along with the beneficial clinical outcomes for ICU patients through repeated measures of REE using IC. The study compared patients who were randomised to either a tight calorie controlled group where daily energy delivered was determined using repeated IC to measure REE or the control group where energy goal was determined once using a weight-based equation (25kcal/kg/day). The authors of the study were able to identify significant daily changes in REE within the first 10 days of ICU admission (P <0.008). Following the intention-to-treat analysis, the intervention group that received nutrition therapy (both enteral and supplemental parenteral nutrition) trended towards lower hospital mortality (P = 0.058). This trend was found to be significant when excluding those lost to follow-up (28.5% for the IC group vs. 48.2% for the control group) (P

= 0.023) and the rate of 60-day survival was significantly greater for the intervention group. The results of this study were able to demonstrate the effectiveness of repeated IC measures to tightly control caloric delivery, thus improving clinical outcomes. However, even with IC being more beneficial in determining patients requirements, there are technical barriers to consider such as the clinicians knowledge of use and interpretation of IC [19,21].

Heyland *et.al.*[4], identified that regardless of the method used to determine requirements, delivery of nutrition closer to target requirements maybe be more clinically significant and meaningful than using IC as a measure of requirements. This data was obtained through the analysis of 3 large observational studies following the INS. This analysis of 7872 mechanically ventilated patients from 335 ICUs in 33 countries in 2007, 2008 and 2009. They found that patients who received at least two thirds of their energy requirements were 33% less likely to die than those who received less than one third of their requirements (OR 0.67; 95% CI 0.56-0.79; $p < .0001$) following adjustments for covariates[4]. The association of reduced mortality and greater requirements achieved using weight-based equations was similar to the results from the multicentre observational study conducted by Alberda *et al.*[2]. From 2772 mechanically ventilated patients from 167 ICUs in 21 countries, they found a reduction in 60-day mortality with every 1000kcal calories and 30 grams of protein received per day. While both studies found clinically significant outcomes, it is important to note that this study was an audit of nutrition practices in ICU and no standardisation in nutrition clinical practices was implemented. However, these studies demonstrated patient clinical outcomes (overall mortality) can be reduced by meeting nutritional requirements, even in the absence of IC.

Nutrition Provision

Within the ICU population, nutrition support is provided in varying methods (oral, tube feeding or intravenous) based on a patient's clinical state. Intubated and mechanically ventilated patients often receive nutrition through a tube and in exceptional circumstances when gut function is poor – intravenously[6,8]. It is often difficult to achieve target nutritional rates due to factors such as postoperative contraindications, gastrointestinal intolerance, cessation of feeding for procedures among others[22 23].

Enteral nutrition is the delivery of oral nutrition supplements through a feeding tube to the gastrointestinal tract[15]. This mode of nutrition delivery has been sought to attenuate the metabolic stress response[3], as well as to maintain the structural and functional integrity of the gut[6-11]. The best practice guidelines for nutritional management in ICU recommend the delivery of early enteral nutrition via the gastrointestinal tract where clinically feasible[6-9].

Early Enteral Nutrition

Critical illness has been associated with changes in the functional and structural integrity of the gastrointestinal tract (GIT), leading to an increase in gut permeability further resulting in more complications including systemic infection and multiple organ dysfunction syndrome[24]. There is strong evidence demonstrating EN reduces the incidence of these complications by preserving the integrity of the GIT[25-27]. As a result, evidence based guidelines recommend early initiation of EN within 24-48 hours of ICU admission where clinically appropriate[6,8,9]. A recent meta-analysis conducted by Doig *et al.*[26] including six trials with a total of 234 patients demonstrated a significant reduction in mortality rates following the initiation of

standard EN within 24 hours of injury or ICU admission (OR=0.34, P=0.02, I^2= 0%) and reduction in pneumonia incidence (OR=0.31, P=0.01, I^2=0%) when compared to delayed EN initiation. These findings were consistent with a similar meta-analysis of 3 RCTs including 126 trauma patients conducted by the same authors demonstrating a reduction in mortality and pneumonia in patients fed early EN within 24 hours P = 0.04 and P = 0.05, respectively[25]. Both studies demonstrated significant reduction in mortality rates and incidence of pneumonia when fed EN early compared to withholding EN. Although, the quality of all trials from both systematic reviews may be questionable as the methodological quality of all trials had a high risk of bias. None of the trials from both systematic reviews provided sufficient information regarding randomisation, none of the trials were blinded, and some were unclear of allocation concealment indicating a risk of performance and selection bias. However, these systematic reviews support the use of initiating enteral nutrition early in critical illness to maintain GIT functional integrity and reduce morbidity and mortality.

Gastric vs Small bowel feeding

Clinical practice guidelines recommend using the gastric route for EN delivery, unless the patient is at risk of aspiration pneumonia[6]. However, research has been conducted on comparing the clinical outcomes for the use of the small bowel compared to gastric route. Deane Adam *et al.*[28] conducted a systematic review to compare the incidence of ICU-acquired aspiration pneumonia in 1178 patients EN fed via the gastric route or in the small bowel. Following the meta-analysis of 15 RCTs, there was a significant reduced relative risk for incidence of pneumonia for small bowel compared to gastric tube fed patients (RR: 0.75; 95% CI: 0.6 to 0.93, P = 0.01) with low heterogeneity between groups (I^2 = 11%). ICU and hospital LOS, duration of mechanical ventilation and mortality were unaffected between the

two groups. These findings are consistent with the systematic review conducted by Sajid *et al.*[29]. When comparing EN via nasogastric to post-pyloric in medical and surgical ICU sites, there was a 41% reduced risk of aspiration pneumonia for small bowel fed patients (OR = 1.41; 95% CI: 1.01-1.98; P = <0.04). In addition, small bowel fed patients had lower gastric residual volumes (GRV) defined as GRV >300-500mL (3.95; 95% CI: 1.19 – 13.14; P = 0.03;) and improved caloric delivery (standardized mean difference = -1.02; 95% CI: -1.73 - -0.31; P<0.005). Although both analyses had significant heterogeneity (I^2 = 73%; P <0.001 and I^2 = 95%; P <0.00009 respectively), which may have been attributed by geographical variation, severity of illness scores and variances in EN management for both medical and surgical patients. Sajid *et al.*[29] were also unable to show a difference in ICU LOS, mortality or incidence of gastrointestinal complications (nausea, vomiting, diarrhoea, abdominal distention, reflux and gastrointestinal bleed). Thus, the benefits of EN delivered via the small bowel (nasojejunal or nasoduodenal) include reducing the risk of pneumonia. However, there is insufficient evidence to suggest the EN through the small bowel improves clinical outcomes (mortality, ICU and hospital LOS). Therefore, small bowel feeding should be considered for those with high risk of aspiration or contraindicated for gastric feeding.

Parenteral Nutrition

The delivery of nutrition support intravenously (parenteral nutrition) is more effective in delivering a greater amount of calories compared to EN. However, EN continues to be the predominant choice as it is associated with more beneficial outcomes for preserving gastrointestinal integrity, maintain homeotic status and suggested to improve patient clinical outcomes (reduced LOS and mortality)[8,9]. However, recent research that argues there is no difference in the association between PN or EN on clinical outcomes (incidence of infectious complications, LOS and mortality) [30].

A recent systematic review by Elke *et al.*[30], conducted a meta-analysis of 3347 ICU patients from 18 randomised controlled trials comparing the effect of EN and PN on clinical outcomes (2016). The meta-analysis found no significant difference on overall mortality, even following subgroup analysis of trials where PN received more calories. There was also no difference in hospital length of stay or duration of mechanical ventilation. However, patients with EN had significantly less incidence of complications associated with infections and reduced ICU LOS. Similar to this review, the large CALORIES study compared clinical outcomes and identified the cost-effectiveness for early nutrition support through early parenteral and enteral nutrition [31]. Conducted as a pragmatic randomised controlled trial in 34 ICU sites including 2383 patients, they found no significant difference in 30-day mortality when comparing early PN delivery to standard care (EN). Patients receiving nutrition support through PN had lower incidences of hypoglycaemia (P = 0.006) and vomiting (P <0.001) compared to EN. Following cost-benefit analysis, the PN group was associated with greater costs compared to EN (£24,458 vs. £23,164) with no significant difference in EQ-5D-5L score (parenteral 0.655, enteral 0.654) or QALYs (parenteral 0.051, enteral 0.050). In conclusion, this study demonstrated no cost-benefit for the use of PN over EN and no difference in quality of life. It is important to note as a pragmatic study, this study did not include standardisation of clinical nutrition practices within each participating ICU, which may be due to the size and nature of the study.

In contrast, there is potential positive outcomes for the use of EN with supplemental PN. A multicentre observational study including 2920 patients from 260 ICUs examined the effect of supplemental PN when comparing early EN alone, early supplemental PN and late supplemental PN[32]. As expected the amount of calories and protein received was significantly

greater in the early PN group (P<0.001). However, when analysing for clinical outcomes, differences favoured the early EN group. Early EN had a significantly lower 60-day mortality rate (27.8%, P=0.02) compared both early and late PN groups (34.6% and 35.3%, respectively), and demonstrated significantly less duration of mechanical ventilation (P = 0.007), and shorter ICU and hospital LOS (P = 0.003 and P = 0.004, respectively). These results are contrasting to the TICACOS study which found a trend in reduced mortality for the use of supplemental PN[20]. Compared to EN or PN alone, the combined use may be considered a more aggressive nutrition therapy. Thus, the indication for its use should be carefully warranted in current practice, however there are current randomised controlled trials focusing on supplemental PN [33,34].

ICU Quality improvement practices – INS & Feeding Protocols/Algorithms

While it is widely recognised that nutrition is an integral therapeutic component of care in the ICU[6], the International Nutrition Survey (INS) identified a high prevalence of underfeeding critically ill patients worldwide[4,35,36]. The INS, a quality improvement benchmarking tool, has been used internationally to model large multi-centred observational studies to compare clinical practices of adult ICUs worldwide [4,35]. An example of this is a large multi-centred observational audit conducted over 202 ICU sites surveying over 26 countries, that found the average energy and protein delivered was approximately 60% of prescribed requirements[36].This is substantially lower than the minimum of 80% shown to be associate with a reduction in mortality[4]. Thus highlighting a large proportion of critically ill patients worldwide who are accumulating an energy and protein deficit.

Moreover, the outcomes for participating in the INS, the clinical practice guidelines along with current research being conducted, assist clinicians to develop feeding protocols to ensure

effective feeding practices and optimal nutrition provision in ICU. An example of this includes the Enhanced Protein-Energy Provision via the Enteral Route Feeding Protocol (PEP-uP) to improve protein and energy delivery in enteral fed ICU patients[35]. Heyland *et al.*[35] conducted a multi-centre observational study examining the implementation of this protocol and has demonstrated significantly greater delivery of prescribed energy (60.1% vs 49.9%, P = 0.02) and protein (61.0% vs 49.7%, P = 0.01) requirements from EN source[35]. Despite the ICU sites implementing the PEP-uP protocol not meeting the 80% of prescribed requirements, this study has demonstrated effective protocol implementation targeting ICU clinicians.

Similar to the PEP-uP study, two cluster-randomised controlled trials[37,38] evaluated the implementation of an evidence-based feeding protocol in intervention ICUs compared to control ICUs. Both studies included multiple strategies to implementing the protocol including adopting an influential opinion leader, providing in-services to ICU clinicians, printed protocol-use reminders and auditing nutrition practices to which they received feedback. Doig *et al.*[37] incorporated additional strategies such as active protocol reminders whereby the investigating ICU dietitian would remind clinicians of the protocol, also used academic detailing where investigators and influencing opinion leaders were trained to facilitate a one-on-one conversation with a ICU staff member unwilling to adopt the protocol. However, only Martin *et al.*[38] was able to demonstrate a trend in the reduction of hospital mortality favouring the intervention group that used an evidence-based protocol (intervention ICUs: 27% vs control ICUs: 37%, P = 0.058) compared to control ICUs. They also found a significant reduction in hospital LOS in the intervention group (35 days in control ICUs vs 25 days in intervention ICUs, P = 0.003). However, these findings may have been influenced following a per-protocol analysis, when 2 sites were excluded in analysis due to inappropriate

randomisation. Doig *et al.*[37] found a significantly greater amount of intervention ICUs received nutritional support (difference: 22.5%; 95% CI: 18.1%% - 25.0%; P<0.001), greater amount fed within 24 hours of ICU admission (difference: 23.4%; 95% CI: 12.9% - 36.2%; *P* <0.001) and fed a greater proportion of ICU days (difference: 1.18 days; 95% CI: 0.41 - 2.03; *P* = 0.002).

More recently Cahill *et al.*[39] conducted an observational study similar to the cluster-randomised controlled trials. The study assessed the feasibility of implementing multifaceted interdisciplinary tailored interventions to 5 ICUs to improve EN delivery. The protocol implementation strategies used were similar to those used in the previous studies [37,38]. However, this study included the identification of barriers through a questionnaire completed by ICU clinicians, scored and ranked by priority, followed by site-specific action strategies targeting each identified barrier. They were able to demonstrate a reduction in overall barriers score with a difference of 10-points. Barrier items showing greatest change included 'delivery of EN to the patient' and 'providers attitude and behaviour'. Although these studies[37-39] did not demonstrate significant outcomes on clinical outcomes, they did highlight the feasibility of implementing a protocol using a multifaceted and interdisciplinary approach for practice change. These studies also demonstrated the potential improvements in clinical practice through the development of feeding protocols.

By continuing to audit and evaluate current practices, gaps in EN performance, barriers in services and knowledge gaps can be identified, thus better inform future research development to improve quality of care.

Original Research Manuscript

This manuscript will be submitted as an original communication to the Journal of Parenteral and Enteral Nutrition.

Abstracts will also be submitted to the 2017 Asia Pacific Conference on Clinical Nutrition (APCCN) and 2017 Australasian Society for Parenteral and Enteral Nutrition (AUSPEN) conference.

The provision of Enteral Nutrition in Critically Ill Patients: The ENCIP Study

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ABSTRACT

Background: Underfeeding is prevalent in intensive care units (ICU), which has been associated with poor clinical outcomes. As a result, feeding protocols have been developed to help improve the efficacy of enteral nutrition (EN) delivery in critically ill patients. *Aim*: The study aimed to assess the adequacy of EN provision in an ICU, following a local feeding protocol. In addition, investigated if the local protocol enabled an association with ICU and hospital length of stay (LOS) and mortality (ICU, hospital and 28-days). *Methods*: A prospective observational study was conducted from October 2016 to February 2017, recruiting ICU patients (>18 years) exclusively EN fed ≥ 24 hours up to 12 ICU days. The main exposure was nutritional adequacy (defined as meeting 80% energy and protein requirements). The primary outcome was adherence of the protocol evaluated through 5 domains: monitoring, prescription, adjustment and referral. Secondary outcomes included ICU and hospital LOS, and ICU, hospital and 28-day mortality. *Results*: A total of 42 medical and surgical patients were included in this study. Only a small proportion (19%) of patients met nutritional adequacy. Evaluation of the protocol provided insights pertaining to the possible reasons for underfeeding, including the slow progression of feeding rates due to low adherence to EN rate changes adjusted appropriately and frequent EN interruptions. No associations were found between hospital- and 28-day mortality and nutritional adequacy. *Conclusion*: Nutritional adequacy was assessed in this study population and the results from the protocol adherence highlighted potential reasons for underfeeding in this study sample.

BACKGROUND

Underfeeding patients in a critically ill state leads to an energy and protein deficit, subsequently contributing to a decrease in lean body mass and malnutrition[6,8]. Malnutrition in critical illness is associated with poor wound healing, increased risk of infection, organ dysfunction, increased duration of mechanical ventilation, and an increase in mortality[4,6,8,36]. The importance of nutrition therapy in critical care has been well established in large observational studies.

The International Nutrition Survey (INS), conducted across 33 countries, with 7,872 participants found mortality rates were 33% lower in patients who received at least two thirds of their energy requirements, in comparison to those who received less than one third of prescribed requirements[4]. Despite this, a high prevalence of underfeeding in critically ill patients worldwide persists. The INS conducted over 202 ICU sites in over 26 countries found that the average energy and protein delivered was approximately 60% of prescribed requirements[36]. This is substantially lower than the 80% of requirements shown to be associated with a reduction in mortality[4], highlighting a need for strategies to optimize nutrition in critical ill patients.

To improve efficacy of nutrition delivery, feeding protocols are routinely modified to account for any significant changes in clinical practice guidelines. Modifications may also be made based on findings from routine audits of feeding practices[40]. Despite efforts to optimise delivery, clinicians are often faced with significant challenges, both procedural and physiological thereby contributing to patients' cumulative energy and protein deficit[23]. Common challenges include gastrointestinal problems, risk of aspiration pneumonia, feeding interruptions caused by procedures, technical issues with feeding access, feeding tube

positioning and intolerance to enteral nutrition (high gastric residual volumes, vomiting and nausea).

This prospective observational study aims to assess the adequacy of EN provision compared to prescribed energy and protein requirements among adults following the local enteral feeding protocol. We also sought to investigate if the local protocol enabled an association with meeting 80% of energy and protein requirements with patient health-related outcomes (length of stay (LOS) and mortality).

METHODS

Subjects and Methods

We conducted an observational study within two ICU sites (public and private) of an Australian tertiary hospital both following a local EN feeding protocol Figure 1 (see Appendix C). Patients from a heterogeneous ICU population of predominantly medical and surgical patients were consecutively enrolled from both ICU sites between October 2016 to February 2017. Patients were deemed eligible if they were ≥18 years and were being tube fed (via a nasogastric tube (NGT), nasojejunal tube (NJT), orogastic tube (OGT), orojejunal tube (OJT), percutaneous endoscopic gastronomy (PEG) or jejunostomy tube) for the primary purpose of providing exclusive EN during ICU admission for at least 24 hours and up to 12 ICU days. Patients not receiving EN or receiving a mixed route of nutrition support (i.e. EN and parenteral nutrition or EN and oral diet) were excluded.

The study was approved by the Mater Human Research Ethics Committee and a waiver of consent was granted.

Data collection

Data collected from day one of ICU admission: demographics including age, gender, ICU site, hospital and ICU admission date and time, reason for admission, comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE) II/III score, need for mechanical ventilation, duration of mechanical ventilation, weight (actual, dry or adjusted), height, and presence of oedema. Outcomes related to nutrition provision, including nutrition prescribed and nutrition delivered from 24 hours up to 12 ICU days or until separated from ICU, was collected prospectively from medical notes and ICU observation charts. Patients discharged from the ICU to a ward were followed-up to establish health-related outcomes (ICU and hospital discharge date and mortality). Data was collected by an independent research dietetics student, with no affiliation with this treating unit.

Nutrition Provision

Nutrition provision measures included estimated energy and protein requirements (EER & EPR) prescribed by the ICU dietitian, charted EN type and goal rate, percent of EER and EPR met, daily EN provision received up to 12 ICU days, reasons for EN adjustment. EER and EPR was calculated using the minimum value in the range provided by weight-based equations (105-125 kJ/kg/day range and 1.2-2.0 g protein/kg/day range, adjusted ideal body weight was used for BMI >30). Percent of EER and EPR was calculated as amount of energy or protein from EN received divided by EER/EPR x100.

Nutritional Adequacy

Nutritional adequacy was defined as meeting ≥80% prescribed energy and protein requirements. This was measured by comparing the mean total daily energy and protein received up to 12 days of ICU EN feeding days to the prescribed estimated energy and

protein requirements. Nutritionally adequate patients were defined as meeting ≥80% prescribed energy and protein for all days of enteral feeding in the ICU. The numerical marker of adequacy (≥80%) is based on international benchmarking standards associated with improved clinical outcomes[4]. Contribution of energy and protein from sources other than EN (propofol and dextrose) were also included into the total daily energy and protein received.

Protocol Adherence

Adherence to the ICU enteral feeding protocol was evaluated using five domains: prescription (EN goal rate, feed type, and rate commenced), monitoring (appropriate frequency and management of aspirate checks as per protocol), adjustment (appropriate changes in EN rate (defined as increased or decreased appropriately or inappropriately following aspirate check), change in feeding tube and correct use of aspirate threshold), referral (timely referrals to physicians), and medication (appropriate administration of motility agents). Adherence to each component of the domains were determined by the criteria outlined in **Table 1**. Reasons for EN rates not changed as per protocol were documented and reasons for EN interruption and duration of interruption were recorded.

Exploratory factors

Other factors influencing nutrition provision and/or surrogate markers of tolerance were explored including: the administration of propofol and dextrose (total mL/day), incidence of hyperglycaemia (defined as blood glucose levels ≥10mmol/L), administration of steroids (dosage and frequency), and the appropriate use of the bowel management protocol. Explanatory variables included: baseline characteristics, nutritional adequacy variables,

severity of illness score /APACHE, temporary EN cessation, hyperglycaemia, steroid administration and appropriate bowel protocol usage.

Table 1. Criteria of assessing adherence of EN feeding protocol domains

Domain	Criteria of adherence
Prescription	
EN goal rate	EN goal rate meets prescribed energy and protein requirements.
Feed type	Feed type suitable for clinical condition (e.g. renal formula for kidney failure).
Commenced rate	Rate commenced at 30mL/hr
Monitoring	
Frequency of aspirates checks	Aspirates checked every 6 hours of EN feeding
Management of aspirates	Aspirate returned if < 300mL If aspirate > 500mL, returned 200mL and discarded remaining
Aspirates Threshold	Correct use of aspirates threshold (300mL)
Adjustment	
Appropriate change in EN rate	Following aspirate < 300mL, increase rate by 30mL/hr, OR Following aspirate < 500mL, decrease rate by 10-20mL/hr, OR Following aspirate > 500mL, cease feeds
Appropriate change in feeding tube	Following > 2 days of high aspirates, feeding tube changed to small bowel feeding tube OR Meeting EN goal rate > 2 days, feeding tube changed to fine-bore tube
Referral	
Timely referral to physician	Referral to physician made following incidence of feeding intolerance (i.e. high aspirates (≥ 500mL), vomiting, distension).
Medication	
Appropriate administration of pro-motility agent	Pro-motility agent administered following 2 consecutive days of high aspirates

EN, enteral nutrition

All patients admitted into ICU requiring EN follow this protocol, except for oesophagectomy patients who do not follow the similar processes in the monitoring domain. Due to differences in feeding management practices (such as aspirates taken more frequently than 6 hours, discarding all aspirates taken, not using an aspirates threshold and being fed through a jejunostomy tube), the oesophagectomy patients were not included in the analysis for the monitoring domain of protocol adherence.

Patient health-related outcomes

The outcome variables included length of stay (LOS) and mortality, both measured in ICU

and hospital to a maximum of 28 days follow-up.

Statistical Analysis

SPSS version 22.0 [2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.] was used for statistical analysis. Descriptive categorical variables were expressed as proportions using chi-squared and means with standard deviations or medians with interquartile range using t-tests or Mann-Whitney *U* test for continuous values, as appropriate. A logistic regression model was used to identify factors associated with the independent factor meeting 80% of energy and protein requirements with outcomes ICU-, Hospital- and 28-day Mortality. A linear regression model was used to evaluate the relationship between the percentage of requirements (energy and protein) met as independent factor with dependent factor ICU or Hospital length of stay. $P<0.05$ was regarded as statistically significant.

RESULTS

From October 2016 to February 2017, a total of 42 patients were exclusively EN fed and were included in this study. The baseline characteristics of the study sample are summarised in **Table 2**. The most common type of admission was medical, with the largest medical groups being respiratory, sepsis and neurological admissions. The most common type of surgical elective admission was oesophagectomy (n=13). Data for duration of mechanical ventilation was missing for one patient, with the median hours of mechanical ventilation being 47.2 hours (IQR: 0.0 – 167.6). The main feeding route for patients were orogastric (42.9%), jejunostomy tube (35.7%) and nasogastric (21.4%).

Table 2. Demographics of ICU patients from October 2016 to February 2017, of the general sample and oesophagectomy patients.

Patient Characteristics	Study sample
Patients	42
Age (mean ± SD)	61 ± 15.3
Sex N (%)	
Male	24 (57.1%)
Female	18 (42.9%)
BMI kg/m^2 (mean ± SD)	25.7 ± 3.8
APACHE II Score (mean ± SD)[a]	18.1 ± 7.3
APACHE III Score (mean ± SD)[a]	63.4 ± 27.4
Type of Admission n (%)	
Medical	24 (57.1%)
Surgical Elective	15 (35.7%)
Surgical Emergency	3 (7.1%)
Medical admission reasons n (%)	
Vascular	1 (2.4%)
Respiratory	10 (23.8%)
Gastrointestinal	1 (2.4%)
Neurological	7 (16.7%)
Sepsis	8 (19.0%)
Metabolic	4 (9.5%)
Hematological	2 (4.8%)
Other	3 (7.1%)
Surgical admission reasons n (%)	
Gastrointestinal	16 (38.1%)
Gynaecological	1 (2.4%)
Orthopedic	1 (2.4%)
Other	1 (2.4%)
Comorbidities n (%)	
Myocardial	2 (4.8%)
Vascular	17 (40.5%)
Pulmonary	13 (31.0%)
Neurological	3 (7.1%)
Endocrine	12 (28.6%)
Renal	4 (9.5%)
Gastrointestinal	18 (42.9%)
Oncology/Immuno	19 (45.2%)
Psychological	2 (4.8%)
Musculoskeletal	4 (9.5%)
Other	3 (7.1%)

APACHE, Acute Physiologic Assessment and Chronic Health Evaluation scoring II & III; BMI, body mass index[weight(g)/height(m^2)]; N, number; SD, standard deviation

[a] missing data of 3 patients for APACHE scores II/III

Nutrition Provision and Adequacy

EN was initiated predominantly within 24 hours (90.5%), with a few patients initiated between 24 – 48 hours (4.8%) and 48 – 72 hours (4.8%). The mean prescribed energy and protein requirements and provision of EN delivered are summarised in **Table 3**. Overall, the percentage of patients who reached EN goal rate during ICU admission was 66.7%. The proportion of patients meeting 80% of energy and protein requirements was 21.4% (n=9) and 31.0% (n=13) respectively. Overall the proportion of patients who met nutritional adequacy from EN received was 19% (n=8). The average percentage of prescribed energy and protein received for the patients that met nutritional adequacy was 92.1% (SD: ± 4.4) and 101.5% (SD: ± 9.3) respectively. The average daily energy and protein received for patients that met nutritional adequacy was 7078.1 kJ (SD: ± 848.5) and 80.9 g (SD: ± 11.0) respectively.

The nutritional provision was different between oesophagectomy patients and the rest of the patient population. There were 13 oesophagectomy patients with a mean age of 67 years (SD: ±5.5), mean BMI of 24.8 kg/m^2 (SD: ±2.4) and mean APACHE II/II scores of 15.3 (SD: ±4.6) and 60.3 (SD: ±26.0) respectively. EN was initiated within 24 hours in all oesophagectomy patients. Compared to the remaining patients, there were significantly fewer oesophagectomy patients that achieved EN goal rate (38.5%, P = 0.009) and significantly fewer that met 80% of energy (0.0%; n=0; P= 0.023) or 80% of protein (7.7%; n=1; P=0.029 respectively) requirements. The average percentage of prescribed energy and protein received was 50.9% (SD: ±15.5) and 56.1% (SD: ±19.5) respectively. When compared to the rest of the sample, these were not significantly different.

Table 3. The nutrition provision and adequacy of EN fed ICU patients

Nutrition Provision	Whole Sample (n=42)
Prescribed EER (kJ/d) (mean ± SD)	8043.1 kJ ± 1612.5
Prescribed EPR (g/d) (mean ± SD)	80.3 g ± 16.7
EN goal rate achieved, n (%)	28 (66.7%)
EN received in 24 hours	
Energy received in 24 hrs (kJ) (mean ± SD)	2362.3 kJ ± 2074.6
Energy (EN + meds) in 24 hrs (kJ) (mean ± SD)	2544.6 kJ ± 2166.7
Percent EER met in 24 hrs (%) median (IQR)	16.3% (10.6 – 50.9)
Met 80% EER in 24 hrs (n, %)	4 (9.5%)
Protein received in 24 hrs (g) (mean ± SD)	26.5 g ± 23.9
Percent EPR met in 24 hrs (%) (mean ± SD)	18.2% (10.7 – 53.0)
Met 80% EPR in 24 hrs (n, %)	5 (11.9%)
EN received in 48 hours	
Energy received in 48 hrs (kJ) (mean ± SD)	3638.7 kJ ± 2034.4
Energy (EN + meds) in 48 hrs (kJ) (mean ± SD)	3978.1 kJ ± 2237.6
Percent EER met in 48 hrs (%) (mean ± SD)	63.7% ± 35.6
Met 80% EER in 48 hrs (n, %)	15 (35.7%)
Protein received in 48 hrs (g) (mean ± SD)	40.9 g ± 23.5
Percent EPR met in 48 hrs (%) (mean ± SD)	69.0% ± 40.9
Met 80% EPR in 48 hrs (n, %)	16 (38.1%)
Average daily EN received	
Average daily energy received (kJ) (mean ± SD)	4557.2 kJ ± 2095.6
Average daily energy (EN + meds) received (kJ) (mean ± SD)	5060.8 kJ ± 2142.6
Percent EER met over total ICU admission (%) (mean ± SD)	57.2% ± 24.8
Average daily protein received (g) (mean ± SD)	50.1 g ± 24.8
Percent EPR met over total ICU admission (%) (mean ± SD)	62.8% ± 28.3

EER, Estimated energy requirements; EN, enteral nutrition; EPR, Estimated protein requirements; IQR, interquartile range; kJ/d, kilojoules per day; Meds, medications (propofol & dextrose); n, number of sample; SD, standard deviation

Reasons for interrupting EN

EN was interrupted in 29 patients (54.8%) of the whole sample, and 7 (87.5%) of the patients meeting nutritional adequacy. Overall, EN was interrupted 71 times with a median of 2 hours (IQR: 0 – 12.1). Reasons for interrupting EN are summarised in **Table 4** with common reasons included '*fasting for bedside procedure*' (26.8%, n=19), '*fasting for extubation or intubation'* (23.9%, n=17) and '*unknown reason for interrupted EN*' (12.7%, n=9).

Table 4. Documented reasons for interrupting EN in the overall sample

Reasons for interrupting EN	% (n)
Fasting for Extubation/intubation	23.9% (17)
Fasting for bedside procedure	26.8% (19)
Fasting for OT procedure	8.5% (6)
Fasting for administration of meds	9.9% (7)
Intolerance to EN (high aspirate volume)	2.8% (2)
Intolerance to EN (abdominal distention)	1.4% (1)
Intolerance to EN (vomiting)	7.0% (5)
Fasting to be assessed by speech pathologist	2.8% (2)
Unknown reason for interrupted EN	12.7% (9)
Commenced TPN	1.4% (1)
Dislodgement of feeding tube	2.8% (2)

EN, enteral nutrition; n, number of incidences; OT, operating theatre; TPN, total parenteral nutrition

Adherence to protocol

Prescription

The EN goal rate and feed type was predominantly recommended by the dietitian (88.1%) and less often by the medical officer (11.9%). The prescribed EN goal rate was 81.0% appropriate and the prescribed EN feed type was 100.0% appropriate. The adherence of commencing EN at 30mL/hour was 59.5%.

Monitoring

The median percentage of patients that was adherent to the frequency of aspirate checks and management of aspirates was 18.2% (IQR: 0.0 – 33.3) and 100% (IQR: 95.8 – 100.0) respectively. The mean percentage of patients that adhered to the aspirates threshold was 96.5% (SD: ± 8.6).

Adjustment

The median percentage of EN rate changes adherent to the protocol was 29.2% (IQR: 0.0 – 66.7). Of the general sample who met goal rate ≥2 days, 8.3% were appropriately changed to a fine-bore tube. There were 147 incidences where adjustment of EN rates changed other than following the protocol. The reasons for changing EN rate other than following the protocol are summarised in Table 5. Common reasons for EN rate changed other than following the protocol for the whole sample included '*EN rate changed later than required*', '*Daily rate set as per Medical officer*' and '*EN rate changed earlier than required*'. '*Rate set as per Medical officer'* was the predominant reason for EN change other than following protocol in oesophagectomy patients.

Table 5. Reasons for changing EN rate

Reason for change	Whole Sample % (n)
Rate changed as per protocol	44.7% (119)
Daily rate set as per MO	28.6% (76)
Change recommended as per dietitian	2.3% (6)
Changed for clinical reasons (e.g. dialysis, fluid overload, etc).	1.1% (3)
Changed due to intolerance (discomfort/abdominal distention/pain)	0.4% (1)
Trophic feeding as per MO	1.1% (3)
No reported reason for change	0.8% (2)
EN rate changed later than required	15.0% (40)
EN rate changed earlier than required	6.0% (16)

EN, Enteral Nutrition; n, number of incidences; MO, Medical Officer

Referral to medical officer

Adherence to the referral domain of the protocol was 100%. A total of 14 patients from the whole sample reported incidences of high aspirates (>500mL) or vomiting. All 14 patients (100%) were appropriately referred to a medical officer.

Medication

Twelve patients (28.6%) from the whole sample were indicated to receive a pro-motility agent due to two consecutive high aspirates (>500mL). Of these patients, 91.7% (n=11) received a pro-motility agent appropriately. Administration of pro-motility agents in oesophagectomy patients was predominantly related to management of nausea.

Other exploratory outcomes

The proportion of the whole sample that were administered propofol or dextrose was 69.0% (n=29) and 78.6% (n=33) respectively, with a median of 3316mL/day (IQR:132.3 – 750.8) of propofol and dextrose administered combined. The incidence of hyperglycaemia occurred in 64.3% (n=27) of the whole sample and 40.5% received insulin therapy. A total of 28.6% (n=12) of the whole sample were administered steroid. The dosages of steroids were 11.9% given <50mg, 4.8% given 50-75mg, 7.1% given 75-100mg, and 4.8% given >100mg. The mean days of steroids administered was 5.3 days (SD: ± 3.1). The bowel management protocol was appropriately used in 4.8% of the whole sample.

Patient health-related outcomes

One patient remained admitted in ICU following data collection and was excluded from ICU and hospital LOS. Overall, the median LOS in ICU and hospital was 7.0 days (IQR: 4.5 – 12.5) and 16.0 days (IQR: 11.0 – 28.0) respectively. For mortality, there was no incidence of mortality in ICU, 1 (2.4%) incidence of mortality in hospital and 2 (4.8%) incidences of mortality at 28-days.

Association with patient health-related outcomes

Following a logistic regression, there was no association between hospital or 28-day mortality and meeting 80% of energy or protein requirements. There was a significant positive association with average percentage of energy requirements met with ICU LOS (regression coefficient = 0.11, 95% CI: 0.06 – 0.17, *P* <0.001), and between average percentage of protein requirements met and ICU LOS (regression coefficient = 0.08, 95% CI: 0.03 – 0.14, *P* <0.005). There was no significant association between average percentage of meeting energy or protein requirements and hospital LOS.

DISCUSSION

In this prospective observational study, we assessed the nutritional adequacy of EN provision in ICU patients following a local protocol. The primary finding was that 19% of patients received adequate nutrition, meeting 80% of energy and protein requirements. Associations between nutritional adequacy and patient health related outcomes were also evaluated, with no association between mortality (hospital and 28-day) and nutritional adequacy (meeting 80% of energy and protein requirements) and a significant positive association between ICU LOS and percentage of energy and protein requirements. Evaluation of the protocol adherence also highlighted specific domains of the protocol where adherence was low, including the frequency of aspirate checks in the monitoring domain, and appropriate EN rate changes and appropriate feeding tube change in the adjustment domain.

In this study, only 19% of the sample met nutritional adequacy, receiving 92.1% and 101.5% of prescribed energy and protein requirements. In comparison, Yip et al.[41] assessed nutritional adequacy of EN fed critically ill patients, defined as meeting 80% of requirements at 72 hours in ICU, following the implementation of a feeding protocol. They found 66% of

patients met energy requirements alone[41]. While Heyland et al.[4] ranked patients nutritional adequacy by tertiles of requirements met, with each tertile specified as meeting one-third (33.3%), between one- and two-thirds (33.3% – 66.6%) and greater than two-thirds (>66.6%) of requirements. They found 40.3% of patients met greater than two-thirds of requirements. In our study, 35.7% of patients received >66.6% of energy and protein requirements, which is only slightly lower than this large observational study. While the performance of nutrition adequacy was lower than Yip et al.[41], the evaluation of the protocol adherence may be able to explain our findings for the proportion meeting nutritional adequacy.

There are many factors in clinical practice which may limit the provision of nutrition including the progression of feeds to goal rate and frequency of EN interruptions. Evaluation of the adherence in the adjustment domain of the protocol identified common reasons EN rates were adjusted other than per protocol. These included 15.0% of rates increased later than required, and 28.6% of rates set daily by the Medical. While over half of the study sample had EN interruptions with a median of 2 hours ceased feeding, with only 66.7% meeting EN goal rate. The most common reasons for EN interruptions in this study sample included 'fasting for bedside procedures' and 'fasting for extubation or intubation'. These findings suggest the combination of low adherence to EN rate adjustments and high incidence of EN interruptions contributed to the slower progression goal feeding rates, which resulted in such a small proportion of patients in this sample meeting nutritional adequacy. This is consistent to the findings of other studies which identified the advancement in EN feeds and EN feeding interruptions to be the greatest contributor to patients not meeting nutritional adequacy[23,40,42]. Peev et al.[23] found patients that experienced at least one interruption were 3 times more likely not to meet nutritional adequacy (<66.6% of requirements). Fasting for procedures and extubation were identified as the most common EN interruptions to EN

provision by Peeve et al.[23] and Chapple et al.[40]. While Kozeniecki et al.[42] identified the initiation and advancement of EN to be the most common reason for sub-optimal intake (<90% of requirements). Together with the findings from this study, this emphasises the technical clinical practice challenges that affect the delivery of optimal nutrition.

Following the investigation of the association between patient health-related outcomes with nutritional adequacy, only the percentage of prescribed energy and protein received was positively associated with ICU LOS. (*Energy:* regression coefficient = 0.11, 95% CI: 0.06 – 0.17, *P* <0.001, and *Protein:* regression coefficient = 0.08, 95% CI: 0.03 – 0.14, *P* <0.005). Similar results were found by Arabi et al.[43] which found an increase in energy intake with an increased ICU LOS. In this current study there are a number of factors that may explain this association. Firstly, two patients were identified as outliers and were excluded in this analysis. Secondly this analysis was not adjusted for known confounding variables such as BMI, age and APCHE II score. Thirdly, the findings of Peev et al.[23] implies the incidence of EN interruptions may also attribute to the increase in ICU LOS. Lastly, as suggested by Heyland et al.[4], less critically ill patients may have shorter ICU LOS, therefore receive little EN.

The association between hospital or 28-day mortality with nutritional adequacy could not be drawn in our cohort of patients'. Heyland et al.[4] found patients meeting two-thirds compared to one-third of prescribed energy and protein requirements was associated with a 33% reduced mortality (*P* <0.0001). Prior studies conducted had larger cohorts of patients, often conducted in multiple ICU sites, included both enteral and parenteral fed patients and were able to find an association or trend between percentage of requirements met and mortality[2,4,38,43]. It is possible that this current study could not draw an association between

hospital or 28-day mortality with nutritional adequacy due to its specific inclusion criteria, where only exclusively EN fed patients were included. This may have limited the inclusion of more critically ill patients, as patients that were parenterally fed, including supplemental parenteral nutrition were excluded.

To the best of our knowledge, this is the first study to evaluate a feeding protocol through 5 specific domains. Other studies have previously assessed the implementation of a protocol by evaluating compliance as an overall percentage[41,44]. By evaluating the protocol in domains, adherence in specific areas which may affect nutrition could more easily identified, such as the adjustment domain as previously described. Although the association between nutritional adequacy and patient health-related outcomes in this study is unclear, the methods of evaluating the protocol by domains may explain the performance of nutritional adequacy in this cohort of patients. Two randomised controlled trials[37,38] investigated the development and implementation of evidence based protocols to improve nutritional support in ICU. Both trials found clinically significant improvements in the delivery of nutrition in patients in the adoption of the guidelines, which were implemented through a multifaceted approach, highlighting the improvement in nutritional adequacy through the use of guidelines. These studies also suggest the use of multifaceted strategies, including the involvement of all ICU clinicians and integration of a multidisciplinary team may be able to effectively address barriers or challenges related to guideline or protocol adherence[45,46], therefore improve nutrition support of ICU patients.

One of the trends identified the analysis was the prevalence of nutrition inadequacy among a particular patient subgroup: oesophagectomy patients. Of the 13 oesophagectomy patients, significantly less met 80% of energy and protein requirements, and significantly less met EN

goal rates. There were no significant differences in baseline characteristics in this subgroup compared with the total sample, and the adherence in appropriate EN rate changes in the adjustment domain of the protocol was similarly low. This very low proportion of these patients achieving EN goal rate or meeting nutritional adequacy may be attributed to two reasons. Firstly, EN rates of oesophagectomy patients were set daily by the medical officer as standard care in this unit due to the nature of the surgery, slowing the progression of feeds to goal rate. Secondly, the evidence for immediate post-operative feeding following oesophagectomy remains unclear. As a result, there is a slower progression of feeding rates in this group of patients, as medical officers may alter rates to reduce the risk of complications following an oesophagectomy. This is an area in need of future investigation, to better understand safe and optimal nutrition feeding practices post-operative for oesophagectomy patients.

The results of this study must be viewed by its strengths and weaknesses. The major strength of this study was the robust methods of data collection conducted by an independent researcher not affiliated with the treating units. The first limitation is the small sample size, which did not allow for a comprehensive adjusted multivariate analysis, limiting its comparability to the existing literature. Broadening the inclusion criteria to include parenteral fed patients, which would increase sample size and possibly conduct more robust analyses. Secondly, the methods of extracting and collecting data in this study heavily relies on documentation provided by the clinical staff. Due to the observational nature study design, it is difficult to control this without influencing clinicians to change practice thus causing desirable outcomes. Lastly, the use of weight-based predictive equations to calculate requirements may not be an accurate measure. The flaws of weight-based predictive equations has been established elsewhere[20], with the potential to over or underestimate

equations due to body weight changes and daily changes in estimate energy expenditure. Indirect calorimetry, ideally would have been used, however it was not feasible to obtain this during the study period. To ensure requirements and calculations were accurate, recent body weights were used and ideal body weight was used in the equation if the patient BMI was >30kg/m^2 and using lower end of requirements to calculate nutritional adequacy.

CONCLUSION

This study found a low proportion of patients EN fed met 80% of energy and protein requirements, which is consistent with the current literature. This result demonstrates a substantial proportion of critically ill patients do not receive adequate nutrition. Furthermore, evaluation of protocol adherence through domains provides novel insights into the specific components of protocol where adherence is low, which may affect the provision of optimal nutrition to critically ill patients. As a result, these findings provide more depth to the reasons behind underfeeding, enabling more specific recommendations to be made in order to change clinical practice and improve the rates of nutritional adequacy in these treating units.

Conclusion & Recommendations

The literature review aimed to provide an overview of current practices in nutrition support, including methods of nutritional assessment in critical illness, early initiation of enteral nutrition, a comparison of parenteral and enteral nutrition and the evaluation of feeding protocols to guide feeding practice. The findings from this review highlighted the challenges in current practice and the gaps in research where more research needs to be conducted.

The observational study aimed to assess the nutritional adequacy of critically ill patients enterally fed following a local protocol. The primary finding was that only a small proportion (19%) of patients received adequate nutrition. Evaluation of the feeding protocol provided additional insights into possible reasons for underfeeding, including the slow progression of feeding rates due to low adherence to EN rate changes adjusted appropriately and frequent EN interruptions.

The study's primary finding is consistent with existing literature regarding the high prevalence of underfeeding patients in ICU[2,4,43]. The results also provided insights into how adherence to protocols can impact the delivery of optimal nutrition, specifically the low adherence of EN rate changes adjusted appropriately slowing progression to goal EN rates. However, it is unclear whether the prevalence in underfeeding is attributed to a gap in clinician knowledge, or due to the paucity of evidence regarding energy and protein requirements during critical illness. Further research needs to be conducted to understand these relationships.

Clinical practice in ICU is informed by evidence based guidelines, which includes the

development of local protocols[6]. The findings of the current study highlighted specific components within the local protocol where adherence was low, which may have contributed to the suboptimal delivery of enteral nutrition. This low adherence may be attributed to clinicians evidence-knowledge gap. To better understand this evidence-knowledge gap, a qualitative study should be conducted to explore the clinicians barriers, issues or challenges to delivering optimal healthcare. This can be achieved through a validated questionnaire[47] or semi-structure interviews to ICU clinicians.

Furthermore, additional research is also required to determine energy and protein requirements during critical illness, especially in the context of the controversial evidence regarding permissive underfeeding and patient outcomes[48]. Therefore, one way to investigate this would be through a 3-arm randomised controlled trial comparing 1) an evidence based feeding protocol and 2) a hypocaloric feeding protocol with 3) a control group, measuring nutrition provision.

The findings from this study also highlighted differences in nutrition provision in oesophagectomy patients compared to the total sample, further highlighting inconsistencies in feeding practices. This may be attributed to the lack of evidence regarding post-operative nutrition support for oesophagectomy patients. Establishing the safety of practices following this procedure may eliminate these inconsistencies, or lead to the development of a more specific protocol subset.

This observational prospective study has not only identified a high prevalence of underfeeding in enterally-fed ICU patients, but also highlighted inconsistencies in the administration of the local feeding protocol. Ongoing research is required to investigate these

inconsistencies to ensure feeding practices and delivery of enteral nutrition follows standardised procedures, so that patients fed through EN are more likely to receive adequate nutrition.

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Appendix A. DAA 2017 Conference Abstract

2017 DAA Conference Abstract Submission

Enteral Nutrition in Critically Ill Patients: The ENCIP Study

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Critically ill patients who receive at least 80% of their energy and protein requirements have been shown to have better clinical outcomes. Mater Health Services (MHS) recently amended their protocol guiding enteral nutrition (EN) delivery in the ICU to optimise nutrition provision; updates included a change in standard formula, reduced frequency of assessing aspirates, a higher acceptable gastric residual volume threshold, earlier introduction of prokinetics, and fewer rate reductions. This study aims to assess the adequacy of EN provision following this protocol. Between October 2016 and February 2017 we are prospectively auditing the process of EN provision in 100 adult patients (≥18 years) admitted into MHS public and private ICUs receiving exclusive EN. To date, 13 of the 100 patients' records have been audited. Descriptive statistics, chi-squared and t-tests will be used to describe the sample, determine if patients received adequate nutrition provision and to identify factors associated with not meeting requirements. Associations between nutrition provision adequacy, factors associated with not meeting energy and protein requirements and length of stay and mortality will be assessed using multivariate linear regression models. This audit will provide insight into the effectiveness of the protocol change, its influence on nutritional adequacy, as well as identify evidence-practice gaps and potential barriers to direct future clinical improvement projects.

Appendix B. Literature Matrix Table

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
Tian et al., (2015) Effect of initial calorie intake via enteral nutrition in critical illness: a meta-analysis of randomised controlled trials	Meta-analysis of randomised controlled trials	Eligibility criteria for studies included randomised controlled trials, randomised trial or study design; adult patients admitted into ICU ≥16 years; intervention groups received two different caloric and protein intakes by EN; and the articles reported clinical outcomes: overall mortality.	Level I Low risk of bias. Used an appropriate selection criteria, included relevant studies, provided an analysis per PRISMA framework.	Issue of interest: optimal amount of calories and protein during critical illness Aim: conduct a meta-analysis of RCTs to identify the optimal amount of calories and protein during critical illness and identify the related clinical outcomes	Mortality was not significantly different for patients in the LE group compared to the HE group (RR: 0.90; CI: 0.71 to 1.15; *P* = 0.40; I^2=31%; *P*= 0.18). Subgroup analysis were performed according to the percentage of goal energy achieved and mortality (groups: <33.3%, 33.3%-66.6% and >66.6%). The subgroup analysis for mortality was significantly lower in the LE group (33.3%-66.6%) (RR: 0.68% 95% CI: 0.51 to 0.92; P = 0.01; I^2 = 0%; P = 0.43). When comparing the HE group to the LE subgroups mortality was not different for groups that were fed <33.3% ((RR, 1.06; 95% CI, 0.86 to 1.31; P = 0.57;I^2 = 0%; P = 0.77) or >66.6% of the goal energy (RR, 1.06; 95% CI, 0.58 to 1.93; P = 0.86; I2 = 31%; P = 0.23). When testing for heterogeneity between subgroups, the heterogeneity among subgroups was high (I^2 = 65.7%, *P*= 0.05). However, when performing the analysis f subgroups based on the differing daily protein intakes, mortality among these subgroups was not different between LE and HE. (I2 = 0%; P = 0.87). Pneumonia: of the studies that reported infections, pneumonia was not statistically different between groups (RR, 1.12; 95% CI, 0.89 to 1.41; P = 0.33; I2 = 0%; P = 0.49). Pneumonia was not affected by percentage of goal energy achieved or the daily protein intake. Gastrointestinal intolerance: ICU LOS: between LE and HE there was no difference in LOS. In addition, following subgroup analysis, the percent of daily energy achieved or daily protein intake did not impact LOS-HOS. Mechanical ventilation: no statistical difference in days of mechanical ventilation between the two groups (HE and LE) (WMD, − 1.04; 95% CI, − 3.29 to 1.20; P = 0.36; I2 = 46%; P = 0.17).	When analysing the difference in infectious complications between LE and HE groups, there was no statistical difference. However, when analysing between subgroups for differing daily protein intakes, infections were lower for those with higher caloric and protein intakes (RR, 1.25; 95% CI, 1.04 to 1.52; *P*= 0.02; I2 = 0%; *P*= 0.41). Although when daily protein intakes were similar, infectious complications were not different between LE and HE groups (RR, 0.94; 95% CI, 0.77 to 1.13; *P*= 0.50; I^2 = 0%; *P*= 0.92). There was significant heterogeneity among the subgroups (I^2 = 77.8%; P = 0.03) The results of the systematic review by Tian et al. (2015) found that mortality was significantly lower for patients that received 33.3% to 66.6% of the target energy compared to the HE group. → could this be attributed by the high heterogeneity in subgroups?? Methodological design

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
Elke et al., (2016). Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials	Systematic Review & meta-analysis	18 RCTs, total number of 3347 patients Critically ill patients >18yrs admitted into ICU Excluded RCTs including pts with elective surgery	Level I	Aim: To compare the clinical outcomes of ICU patients receiving EN vs PN Study inclusion: RCT with parallel group Studied critically ill patients ≥18y – if population unclear, mortality rate higher than 5% in control group considered consistent with critical illness Intervention: EN vs PN reported overall mortality or clinically relevant outcomes including ICU- and hospital-LOS, duration of mechanical ventilation, incidence of infections Exclusion: Elective surgery patients Two independent reviewers, scored trials using scoring system 0-14 based on: randomisation concealment, blinding, analysis based on Intention-to-treat (ITT), comparability of groups at baseline, extent to follow-up, description of treatment protocol, co-interventions, definition of clinical outcomes. Disagreement resolved by consensus Primary outcomes: overall mortality – include ICU, hospital & 28-day mortality Secondary outcomes: ICU-LOS & Hospital LOS, duration of mechanical ventilation, incidence of infectious complications Subgroups: Caloric intake Year of publication Trial methodology	Effect of EN vs PN on mortality No difference in overall mortality between groups receiving EN or PN (RR 1.04, 95% CI 0.82 – 1.33, P= 0.75, I^2= 11%). Following subgroup analysis for caloric intake across groups, no effect on mortality was seen in trials where PN group received significantly more calories that the EN group (RR 1.58, 95% CI 0.75-3.35, P=0.23, I^2= 48%) Effect of EN vs PN on infectious complications EN was associated with significantly reduced infectious incidences compared to PN (RR: 0.64, 95% CI: 0.48-0.87, P= 0.004, I^2= 47%. Following subgroup analysis for 5 trials which the PN group had a significantly higher caloric intake, EN was associated with a significantly lower incidence of infections (RR: 0.55, 95% CI: 0.37-0.82, P= 0.003, I^2= 0%). When subgroup analysis was grouped for the 5 trials where caloric intake was similar between EN and PN groups, thre was no significant difference (RR:0.94, 95%CI: 0.8-1.10, P= 0.003). Effect of EN vs PN on ICU and hospital LOS EN was associated with a significant reduction in ICU LOS (WMD: -0.80, 95%CI: -1.23 - -0.37, P= 0.0003, I^2=0%). Following subgroup analysis for caloric intake, the significant difference was not observed in the two trials where caloric intake was similar between EN and PN groups (RR -0.47, 95%CI: -2.23 – -1.29, P= 0.60, I^2= 8%). No significant difference between EN and PN for trials that reported hospital LOS (WMD: 0.67, 95%CI:1.57-0.24, P= 0.15, I^2 = 2 %), even following subgroup analysis for caloric intake, no significant difference was found Effect of EN vs PN on mechanical ventilation Of those that reported on mechanical ventilation (4 trials), no effect was observed	There is no statistical difference in mortality between the use of EN compared to PN. There was a lower incidence of complications with the use of EN compared to PN. EN should continue to be firstly recommended when possible, as there is no solid evidence for the use of PN over EN.

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
Harvey et al. (2016). A multicentre, randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of early nutritional support via the parenteral versus the enteral route in critically ill patients (CALORIES)	Pragmatic, multicentre, RCT	2383 patients 34 ICU sites	Level II	Aim: determine the effect of PN nutrition support on 30-day mortality. In addition determine cost-effectiveness of PN compared to EN Primary outcome: 30 day mortality	Primary outcome – 30-day mortality 393 (33.1%) patients in the parenteral group had died and 409 (34.2%) patients died in the enteral at 30 days. There was no significant absolute risk reduction in 30-day mortality for PN vs EN (absolute risk reduction of 1.15 percentage points [95% CI −2.65 to 4.94; $p = 0.57$] and a relative risk of 0.97 (95% CI 0.86 to 1.08)). This difference remained non-significant after adjustment for baseline characteristics (odds ratio 0.95, 95% CI 0.79 to 1.13; $p = 0.55$). Secondary outcomes Compared to EN, the PN group had significantly lower incidences hypoglycaemia ($p = 0.006$) and vomiting ($p < 0.001$). There was no statistically significant interaction between the effect of treatment group on 30-day mortality Adherence to protocol Overall adherence to delivery of nutrition support for both groups were high Predominant reason for non-adherence in both treatment groups was treatment withdrawal or death Cost-benefit analysis Compared to EN, PN at 90-days had a higher mean of total cost per patient (£24,458 vs. £23,164). There was no significant difference in EQ-5D-5L score (parenteral 0.655, enteral 0.654) and QALYs (parenteral 0.051, enteral 0.050).	There is no difference in mortality at 30 days between PN and EN. Costs for PN were higher As this evidence does not provide compelling evidence to encourage the use of PN, EN should remain the first-line nutrition therapy in critical illness when indicated. No standardisation of ICU protocol use, or clinical nutrition practices was involved.
Ridley et al. (2015). Supplemental parenteral nutrition in critically ill patients: a study protocol for a phase II randomised controlled trial	Prospective, multi-centre RCT	No participants recruited yet Admitted between 48-72 hours, ≥16 years, mechanically ventilated, PN venous access, ≥1 organ failure,	Not conducted yet	Aim: determine if prescribed energy and protein requirements can be achieved through supplemental PN Primary outcome: mean energy delivered from nutrition therapy over first 7 ICU days Secondary outcomes: Protein delivered in the first 7 days Energy delivered in the ICU stay (up to 28 days) Protein delivered in the the ICU stay (up to 28 days) Total antibiotic usage Sequential Organ Failure Assessment scores Duration of mechanical ventilation	No results published	

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
				Duration of ICU and hospital stay Mortality to 180 days Functional and quality of life to 180 days post randomisation		
Doig et al. (2013).Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial	Multicentre, single blind RCT	1372 patients	Level II Allocation concealment maintained Randomisation within site stratified by age & BMI Single-blinded Intention-to-treat analysis	Aim: to determine the outcomes of ICU patients receiving early PN with contraindications of EN Intervention groups: pragmatic standard care Early parenteral nutrition Primary outcome: 60-day mortality Secondary outcome: Quality of life and physical function measures (RAND-36 general health status and physical function plus plus Eastern Collaborative Oncology Group performance status); clinically significant organ failure; infection rates; ICU and hospital LOS; vital status at ICU and hospital discharge; duration of mechanical ventilation; days of renal replacement therapy; days of pressure ulcers treatment; days of antibiotic use; SGA	Primary outcome – crude 60-day mortality There was no significant difference in 60-day mortality between standard care and the early PN groups (22.8% [155/680] for standard care vs 21.5% [146/678] for early parenteral nutrition; RD, -1.3; 95%CI, -6.6% to 4.1%; *P*=0.60) This remained not significant following adjustment for covariates (age, BMI, APACHE II score, chronic liver disease, chronic lung disease and source of ICU admission) Secondary outcome The PN group had a significant improvement in RAND-36 general health status (QoL) compared to standard care patients (45.5 for standard care vs 49.8 for early parenteral nutrition; mean difference: 4.3; 95%CI: 0.95 to 7.58; *P*=0.01) – however, this improvement was not deemed clinically meaningful/significant The PN group had a significantly reduction days of mechanical ventilation (1.07 days) compared to standard care (-0.47 days per 10 patient ICU days; 95%CI: -0.82 to -0.11; *P*=0.01) Significantly fewer days (0.43 days) of coagulation failure No significant difference in incidence of infections Significantly greater amount of standard care patients had greater muscle wastage (0.43 vs 0.27 increase in SGA score per week; mean difference, 0.16; 95% CI: 0.038 to 0.28; P = 0.01) and significantly greater fat loss (0.44 vs 0.31 increase in SGA score per week; mean difference, 0.13; 95%CI: 0.01 to 0.25; P=0.04)	As with other current literature and the recommendations in the guidelines for critical illness, EN should be first-line nutrition therapy when indicated as there is no compelling evidence to demonstrate better outcomes (mortality) with PN.

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
Mittal et al., 2014 Redefining the gut as the motor of critical illness	Review	n/a		Purpose of review: to highlight new insights into the complex balance that exists between the gut epithelium and the intestinal microbiome, and how perturbations in this relationship can lead to significant morbidity or even death.	n/a	Critical illness and sepsis causes alterations to the integrity of the gut through a cascade of multiple physiological pathways including altered redox reactions, reduced proliferation of epithelial cells and apoptosis progression (cellular death of). The gut has been sought to have induce multiple organ dysfunction syndrome among critically ill patients.
Doig et al (2009) Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials	Systematic Review: meta-analysis	6 RCTs included, total 234 patients Patients included: ventilated medical and surgical ICU patients, burn patients, had severe pancreatitis and/or peritonitis and trauma patients	Level I Selected study Validity: All 6 trials were unclear in detail of method of randomisation none reported blinding All reported complete follow-up	Purpose: determine whether provision of early EN confers treatment benefits to critically ill patients Inclusion/exclusion criteria: Early EN defined as provision of standard EN formula via any feeding tube within 24 hours of initial injury Standard EN formula = formula not supplemented with additional glutamine, arginine or other immune enhancing ingredients Validity/Appraisal methods: At least 3 reviewers Validity determined by majority decision prevailed. Quality appraisal criteria: (1) maintenance of allocation concealment; (2) use of any form of blinding and; (3) completeness to follow-up *Primary outcomes:* Clinically meaningful patient oriented outcomes: mortality, quality of life and physical function *Secondary outcomes:* vomiting/regurgitation,	Mortality Following meta-analysis and test for heterogeneity, there was a statistically significant reduction in mortality in favour of early standard EN (OR=0.34, p=0.02, I= 0%) Secondary outcomes No significant difference in vomiting rates (0/10 early EN patients vs. 1/10 delayed EN, Fisher's exact P = 1.00). (Only one study reported measures of vomiting – included burn ICU patients) Among two trials reporting incidence of pneumonia, there was a statistically significant reduction in pneumonia incidence for patients with early EN (OR=0.31, p=0.01) with no evidence of heterogeneity (I^2=0%) For the one trial that reported incidence of positive blood cultures, there was no significant difference in positive blood culture rates between groups (3/10 early EN patients vs. 7/10 delayed EN, Fisher's exact P = 0.18). No trials reported incidence of sepsis Of the two trials reporting incidence of MODS, there was no significant difference between groups. However, one of these trials which reported the severity of MODS demonstrated a trend towards fewer failed organ systems for those with early EN (2.5 ± 0.7 vs. 3.1 ± 0.8 organ failures per patient, P = 0.057).	Commencing feeds within 24 hours of injury or ICU admission may reduce the rate of mortality of critically ill patients

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
				pneumonia, bactraemia, sepsis and multiple organ dysfunction (MODS)		
Doig et al., (2011). Early enteral nutrition reduces mortality in trauma patients requiring intensive care: A meta-analysis of randomised controlled trials	Systematic Review: meta-analysis	3 Randomised Controlled Trials 126 Trauma patients	Level I All 4 eligible studies provided insufficient detail for randomisation method Unclear allocation concealment None reported blinding Only 3 studies reported complete follow-up – these 3 studies were included for meta-analysis Sensitivity analysis was conducted for all studies identified to be on-topic but methodologically unsound	Purpose: determine whether the provision of early standard enteral nutrition (EN) confers treatment benefits to adult trauma patients who require intensive care. Inclusion/exclusion criteria: Early EN defined as provision of standard EN formula via any feeding tube within 24 hours of initial injury Standard EN formula = formula not supplemented with additional glutamine, arginine or other immune enhancing ingredients Control groups considered: include all forms of standard care, including standard EN provided later than 24 hour after injury Primary outcomes mortality, quality of life and physical function Secondary: vomiting/regurgitation, pneumonia, bacteraemia, sepsis and multiple organ dysfunction syndrome (MODS).	Mortality The provision of early EN within 24 hours had a significant mortality reduction (OR = 0.20, *P*= 0.04, I=0). Secondary outcomes – No included trials reported incidence of vomiting/aspiration, bactraemia or sepsis. Incidence of pneumonia was significantly lower in patients with early EN within 24 hours of injury. (9/27 vs. 16/25, P = 0.050). No significant difference in incidence and severity of MODS Sensitivity analysis of all studies including studies that were methodologically poor demonstrated a significant reduction in mortality for early EN (OR=0.26, P=0.04, I^2=0).	Delivery of early EN (within 24 hours) reduces the risk of mortality in trauma patients The association of early EN with complications (vomiting, aspiration and infections) is still unclear

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
Lew et al. 2016. Association Between Malnutrition and Clinical Outcomes in the Intensive Care Unit: A Systematic Review	Systematic Review	20 Prospective cohort studies	Level I (poor quality Systematic review – only includes prospective studies)	Aim of review: determine independent association between nutrition status and clinical outcomes	SGA: malnutrition identified via SGA was associated with higher hospital mortality, longer ICU LOS and incidence of infections MNA not associated with clinical outcomes NRS: two out of the five had low risk of bias – unclear association with risk of mortality MUST: malnutrition identified via MUST was associated with 1 year discharge mortality	Malnutrition assessments were associated with mortality. Using NRS of NUTRIC can be used in the ICU setting. The categories of SGA provided better predictive validity
Heyland et al. (2011). Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool	Prospective Observational Study	597 patients from 3 tertiary surgical-medical ICUs ≥18 years admitted into ICU within 24 hours Exclusion: elective surgery patients, admitted with an overdose, and patients with an expected ICU admission <24hours	Level III	Aim: purpose of the study was to develop and validate a method (the NUTRIC score) for quantifying the risk of poor clinical outcomes that could be positively influenced/changed by nutrition therapy in ICU. Researcher interviewed family members to collect data of nutrition variables (recent decrease in oral intake (% in last week) and history of weight loss over past 6 months) Inflammatory markers: Blood samples were taken on enrollment and daily until ICU discharge, death or a maximum of 10 days. Samples analysed C-reactive protein (CRP), procalcitonin (PCT),	28-day mortality was significantly associated with all variables except BMI, CRP, % oral intake in prior week and % of weight loss in previous 3 months (P<0.001). All variables except BMI were significantly associated with ventilator-free days within 28 days	Large amount of missing data (oral intake in prior week, and % of weight loss in previous 3 months).

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
Coltman et al. (2014). Use of 3 tools to assess nutrition risk in the intensive care unit	Prospective observational quality improvement project	294 surgical, medical and neuroscience ICU patients Inclusion: ≥18 years Able to communicate in English	Level III	Aim: to compare the proportion of ICU patients identified as at high risk or malnourished using 3 tools: 1) institutions routine screening method; 2) the NUTRIC score; and 3) the Subjective Global Assessment (SGA) Screening using the three tools was conducted by 4 trained Dietitians Routine Screening tool – SGA – completed by ICU dietitians within 24 hours NUTRIC score	A total of 139 ICU patients were identified as at risk of malnourished using at least 1 tool. 63% (87/139 patients) were at risk found using the routine screening tool 80% (111/139) were identified as malnourished using the SGA 26% (36/139) were identified as at risk using the NUTRIC score Only 9 patients (6%) were at risk or malnourished following the criteria of all three tools.	The patients of this ICU are from surgical, medical and neurosciences thus the results of this study may not be applicable to other institutions that include trauma, burns and other units.
Sheean et al. (2010). Nutrition assessment: the reproducibility of subjective global assessment in patients requiring mechanical ventilation	Cross-sectional observational study	57 ICU patients ≥18 years Mechanically ventilated >48hrs	Level III	Aim: determine the reproducibility of the Subjective Global Assessment (SGA) in mechanically ventilated patients. Two registered dietitians that had undergone formal SGA training assessed and categorised patients as (A) normally nourished, (B) moderately malnourished, and (C) severely malnourished using the SGA and within 48 to 96 hours of mechanical ventilation Methods of standardisation for data collection: Weight and diet history (previous nutrition therapies, frequency of hospitalisation) was obtained using the hospital's food and nutrition management software Physician's complete history and physical was used to determine body weight changes, gastrointestinal (GI) symptoms and functional capacity Critical care nursing admission assessments were used to identify body weight, GI symptoms and issues with eating (chewing and swallowing) Fat loss, muscle wasting and signs of oedema were subjectively	Greater than 50% of all patients (n=29) were classified as moderate or severely malnourished. Both agreement and Inter-rater reliability were high (k=0.90) between dietitian raters. Only three patients (5%) were classified as severely malnourished, while the remainder (n=26, 45.6%) were moderately malnourished Malnourished patients had a significantly longer stay in hospital prior to ICU admission, had a reported weight loss prior to ICU admission and poor dietary intake (P<0.0001 and P<0.0001 respectively) Malnourished patients had a greater amount GI symptoms (at least one), with the incidence of diarrhoea and anorexia being statistically significant (P=0.05 and P=0.03 respectively).	High risk for measurement bias – subjectivity for changes in body weight reported by physician and the subjective measures for fat loss, muscle wasting and fluid accumulation (oedema, ascites and sacral oedema).

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
				measured. Specific attention was made to the temporal, clavicular and costal areas as they are less likely to be influenced by fluid accumulation Oedema and ascites was identified by visual inspections while sacral oedema was reported by the caring critical care nurse		
Singer et al., 2011. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients	Prospective RCT	130 patients All 18yo adm into ICU, mechanically ventilated and expected to stay in ICU >3days	Level II Appropriate randomisation States study was not blinded.	Aim: determine whether nutritional support guided by repeated measures of Resting Energy Expenditure (REE) by indirect calorimetry (IC) improves outcome of critically ill patients Primary outcome Whether nutrition support guided by repeated REE improve patient survival Secondary outcomes: 1) length of mechanical ventilation, of ICU and hospital stay; ICU mortality; (2) development of new pressure sores; (3) requirement for unplanned surgery and surgical complications; (4) the incidence of renal impairment, defined by an increase of serum creatinine greater than 1.2 mg/dL or requirement for renal replacement therapy; and (5) the incidence of new onset liver impairment, defined by an increase of total bilirubin greater than 1.2 mg/dL; and (6) infectious complications Study group: EN delivered based on repeated measures of REE from IC	Energy targets from IC group changed significantly over the first 10 days ($p<0.008$). Energy intake among control group was lower than calculated energy targets over entire period Mean daily caloric intake was significantly higher in the study group ($p=0.001$) from both EN and PN Significantly more patients in the study group received PN during the first 3 days Mean daily energy balance was significantly more positive in the study group ($p=0.001$) Mean daily protein intake was significantly higher in study group ($p=0.001$) No difference in the blood glucose levels ($p=0.15$). Primary outcome The study group demonstrated a trend towards lower mortality in the hospital ($p=0.058$) for the intention-to-treat group Per protocol group showed significantly lower hospital mortality ($p=0.023$) 60d-day survival was $57.9 \pm 9.9\%$ in the study group and $48.1 \pm 7.6\%$ in the control group ($p = 0.023$). Secondary Outcomes ICU mortality was not significantly different Length of ventilation and ICU stay were both significantly longer in the study group ($P=0.01$ and $p=0.02$) and total infection rate ($p<0.05$). Higher incidence of VAP in the study group ($p=0.08$). Comments	Indirect calorimetry may be able to improve nutritional adequacy as it is more accurate in identifying REE, including daily REE changes

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
				Control group: EN delivery according to 25kcal/kg/day Preadmission weight determined either by patient or close family member	Hospital mortality was significantly reduced following more accurate methods of defining energy targets and intense nutrition therapy (EN plus supplemental PN).	
Alberda et al. (2009). The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study	Multicentre observational study	21 countries, 167 ICUs 2772 mechanically ventilated ≥18 years of age, mechanically ventilated within 48 hours of ICU admission and remained in ICU for at least 72 hours	Level III	Aim: examine the relationship of energy and protein delivery and clinical outcomes, and the extent to which pre-morbid nutritional status influenced this relationship Nutrition therapy included Enteral nutrition (EN) and Parenteral Nutrition (PN)	The percentage of energy and protein requirements met from nutrition therapy (both EN & PN) was 59.2% and 56% respectively. Average morning blood glucose levels ranged from 7.3 to 8.0mmol/L and were significantly different for all groups Greater amount of calories and protein delivered was associated with a significant reduction in overall mortality (adjusted OR for 60-day mortality for every 1000cal/day was 0.76 (95%CI: 0.61-0.95, *P* =0.014), adjusted OR for 60-day mortality for every 30 g protein was 0.84 (95%CI: 0.74-0.96, *P*= 0.008)). The association of reduced mortality and greater calories and protein delivered was most observed in patients with BMI ≤ 25 and ≥35 There was an association of a 3.9 decrease (unadjusted OR) in ventilator free days and an increase of 1000kcal/day (95%CI: -5.1 – 1.5, *p*<0.001). However, following adjusted analysis an increase of 1000kcal/day was associated with an increase of 3.5 ventilator free days (95%CI: 1.2 – 5.9, *p* = 0.003).	Increased energy delivery, closer to prescribed requirements is associated with reduced mortality.
Peake et al. (2014). Use of a concentrated enteral nutrition solution to increase calorie delivery to critically ill patients: a randomized, double-blind, clinical trial	Multi-centre, randomised, double-blind, parallel-group trial	5 Australian ICUs 112 mechanically ventilated ICU patients receiving EN ≥2d	Level II Clear description of randomisation Allocation concealed Patients, clinicians and study personnel were blinded Blinding of enteral solutions was confirmed in a formal bedside study Intention-to-treat (ITT) analysis	Aim: determine whether the substitution of a concentrated enteral nutrition solution (1.5kcaL/mL) for a standard solution (1.0kcal/mL) would result in greater calorie delivery in ICU patients. Also establish the feasibility of conducting a multicenter, double-blind, randomized trial to evaluate the effect of an increased calorie delivery on clinical outcomes. Feeding goal rates were calculated as 1mL/kg ideal body weight (IBW)/hr Maximum enteral feeding rate was 100mL/hr to reduce incidence of	Primary outcomes Compared to the 1.0kcal/mL group, there was a significantly greater daily calorie delivery in the 1.5kcal/mL group (*P*<0.001). Significant difference between groups for calorie delivery, with the 1.5kcal group receiving a greater amount of calories (1.5kcal group – 1832kcal, 95%CI: 1681, 1944kcal and 1.0kcal group – 1259kcal 95%CI: 1143 – 1374) (*P*<0.001) Significant difference in the proportion of prescribed calories being met from EN was 102% and 72% for the 1.5kcal and 1.0kcal groups respectively (*P*<0.001). A greater amount of patients in the 1.5kcal group met the prescribed calorie requirements on one or more study feeding day (89% vs 16% for 1.5kcal and 1.0kcal groups respectively). Protein delivery between groups were the same	The use of concentrated energy nutrition formula, will improve energy provision. There is a reduced risk of 90-day mortality with concentrated energy nutrition formula (1.5kcal/ml)

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
				overfeeding EN could be ceased if goal rate was achieved for 5 consecutive days To calculate calorie delivery for patients that required PN, it was assumed that EN solution was based on 1.25kcal/mL Patients were randomised to either 1.5kcal/mL or 1.0kcal/mL EN solutions Primary outcome: daily calorie delivery (kcal/day) from EN Secondary outcomes: 1) daily total calorie delivery from EN/PN and incidental calories; 2) daily enteral and calorie delivery calculated per IBW (kcal/kg/d); 3) ICU and hospital LOS; 4) ventilator free days (VFD); 5) ICU, hospital and 28- and 90-day mortality	The 1.5kcal group had a significantly greater of EN calories delivered per kg of IBW (P<0.001) Secondary outcomes A greater number of patients in the 1.0kcal group died at 90 days compared to the 1.5kcal group (20%, n=11 and 37%, n=20 respectively) (P = 0.057). Absolute risk reduction for the 1.5kcal group versus the 1.0kcal group was 17% (95%CI: 0.6 – 33). There was a longer survival time from day 1 to day 90 of study for the 1.5kcal group (P=0.057) ICU and hospital 28 day mortality was not significantly different	
Doig et al., 2008. Effect of Evidence-Based Feeding Guidelines on Mortality of Critically Ill Adults	Cluster randomised trial	1118 critically ill adults exected to memain in ICU >2 days were enrolled from 27 ICUs from Australia and New Zealand.	Level II Clear description of randomisation Appropriate randomisation Maintained blinding No patients lost to follow up	Aim: determine whether evidence-based feeding guidelines, implemented using a multi-faceted practice change strategy, improve feeding practices and reduce mortality in ICU patients. Participating ICUs were randomised to guideline or control groups *Intervention group:* developed an evidence-based guideline using Browman's Clinical Practice Guideline Development Cycle *Outcome measure:* (1) hospital dsc mortality; (2) ICU and hospital LOS, organ dysfunction and feeding process measures. Overall study design: 5 week study run-in and guideline development period 20-week guideline implementation and evaluation Dietitians and intensivist	There was significantly greater amount of patients in the Guideline ICUs that received nutritional support (94.3% vs 72.7%; difference, 22.5% [95% CI, 18.1% to 25.0%]; P<0.001) Significantly greater amount of patients fed within 24 hours of ICU admission (60.8% vs 37.3%; difference, 23.4% [95% CI, 12.9% to 36.2%]). Guideline ICU patients were fed significantly earlier (0.75 vs 1.37 mean days to start of enteral nutrition; difference, −0.62 [95% CI, −0.82 to −0.36]; P_.001 and 1.04 vs 1.40 mean days to start of parenteral nutrition; difference, −0.35 [95% CI, −0.61 to −0.01; P=.04) and fed a greater proportion of ICU days (8.08 vs 6.90 fed days per 10 patient-days; difference, 1.18 [95% CI, 0.41 to 2.03]; P=.002) No significant difference in mean energy delivered per patient/day & mean energy delivered per fed patient/day There was no significant difference in hospital dsc mortality (difference: 1.4%, P= 0.75), ICU dsc mortality (diff: 3%, P=0.43) and hospital or ICU LOS (diff: -0.08, P=0.97 and diff: -0.9, P=0.42, respectively). There was a significantly lower incidence of renal dysfunction among patients in the Guideline ICUs (1.54 vs renal dysfunction days/10 patient days;	The implementation of an evidence based guideline, using a multifaceted approach, can improve the nutrition provision in ICU patients. Although, its association with reducing mortality is unclear. The multidisciplinary approach to develop the guideline can improve clinical practice by providing guidance to clinicians

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
				coinvestigators of the intervention ICUs attended a 2-day guideline development conference Guideline Implementation strategies Guideline conference Influential opinion leader Educational outreach visits Academic detailing Active Reminders Audit & Feedback Passive Reminders In-servicing	difference, −0.58 [95% CI, −1.0 to −0.04]; P=.04)	
Martin et al. 2004. Multicentre, cluster-randomized clinical trial of algorithims for critical-care enteral and parenteral therapy (ACCEPT)	Cluster Randomized controlled trial	>16 years expected ICU stay >48 hours *Exclusion:* Meeting EER & EPR orally within 24 hours of ICU adm, palliative, moribund, not expected to survive for more than 6 hours or brain dead	Level II Clear description of randomisation Appropriate randomisation Not clear if blinding occurred Per-protocol analysis – 1 ICU declined to be assigned as an intervention group but agreed to collect data for control group. Similar ICU with similar stratification factors was assigned to intervention group.	Aim: develop an evidence based guideline to improve nutrition provision Prior to implementing the study, a literature review was conducted using the Browman and colleagues' Clinical Practice Guideline Development Cycle to form recommendations within a protocol/ algorithm regarding the delivery of EN (an PN where appropriate). An evidence-based consensus conference was held where intensivists, gastroenterologists, dietitians and epidemiologists. The protocol developed would later be implemented in the intervention ICUs along with the use of multiple practice change strategies. *Implementation of protocol/algorithm:* used multiple approaches for practice change to implement protocol recognised academic opinion leaders (intensive care physicians from coordinating centres and epidemiologists managing the RCT) provided an in-service to about the protocol recommendations, evidence supporting recommendations to all ICU staff (nurses, physicians, dietitians,	Baseline characteristics Significantly more patients in Intervention group had emergency surgery Primary outcomes Following per-protocol analysis (two inappropriately randomised sites excluded), the was a trend of reduced mortality favouring the intervention group Per-protocol analysis adjusting for type of admission (Elective operative, emergency operative, or other) the reduction in mortality was statistically significant in intervention hospitals (p=0.035) Compared to the control ICUs, there was a significant less amount of mean LOS days (10 days' difference) in the Intervention ICUs (p=0.003). However, there was no statistical difference in ICU LOS between groups. Following per-protocol analysis, patients in the intervention ICUs received significantly more days of EN (6.7 v. 5.4 per 10 patient-days at risk, p= 0.042) and significantly more days of any feed (8.5 v. 6.9 per 10 patient-days at risk, p= 0.02) There was no significant difference shown between groups for the total amount of energy delivered per patient-day, time from ICU admission to receiving enteral feeds, time required to achieve 80% of the calculated energy goal and the number of days on which 80% of the goal was achieved.	The success of implementing an algorithm or protocol should use a multifaceted approach using similar techniques/approaches (highly influential/recognised academic opinion leaders to provide in-services, educational outreach visits and auditing. Early EN resulted in 10% reduction in hospital discharge mortality (univariate p=0.058, multivariate analysis controlling for baseline imbalance p=0.035).

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
				respiratory therapists). Laminated copies of the protocol posted in ICU Pocket card protocols were provided to dietitians to give to nurses and physicians To optimise compliance with protocol the dietitian audited the daily nutrition provision of patients, which would be relayed back to caring team To standardise type of EN feed, a closed EN-system was provided to all ICUs for the study (Ultrapak; Nestle Clinical Nutrition, Toronto, Ont.). *Primary Outcomes:* Hospital mortality, ICU and hospital LOS,		
Cahill *et al*. (2014). Implementing a multifaceted tailored intervention to improve nutrition adequacy in critically ill patients: results of a multicenter feasibility study	Prospective before and after study	5 participating ICU sites	Level IV	Aim: assessing the effectiveness of a multifaceted interdisciplinary, tailored intervention to improve EN provision in ICU An interdisciplinary team was formed at each participating ICU site, which included the ICU dietitian, physician and a nurse. All members self-identified as nutrition opinion leaders. The team roles included study coordination, data collection and implementing the intervention. Intervention modelled by Graham and colleagues 'knowledge-to-action' model Barriers to adherence to critical care nutrition recommendations was assessed using a framework – mitigation of these barriers was informed by Gurses and colleagues 'Barriers Identification and Mitigation Tool' Intervention included: 1) Auditing nutrition performance and	2 of the 5 sites showed a success of implementing an algorithm or protocol should use a multifaceted approach using similar techniques/approaches (highly influential/recognised academic opinion leaders to provide in-services, educational outreach visits and auditing. Early EN resulted in 10% reduction in hospital discharge mortality (univariate p=0.058, multivariate analysis controlling for baseline imbalance p=0.035). >10% increase in calories received interdisciplinary team were able to identify barriers, provide action plans and implement them. There was a decrease in prioritised barriers – reflecting positive impact from the tailored action items	Implementing the barriers to adherence questionnaire has low response rates (24% in this study) The questionnaire was able to highlight barriers and then provide actions to improve clinical practice. Further research is needed to investigate its feasibility.

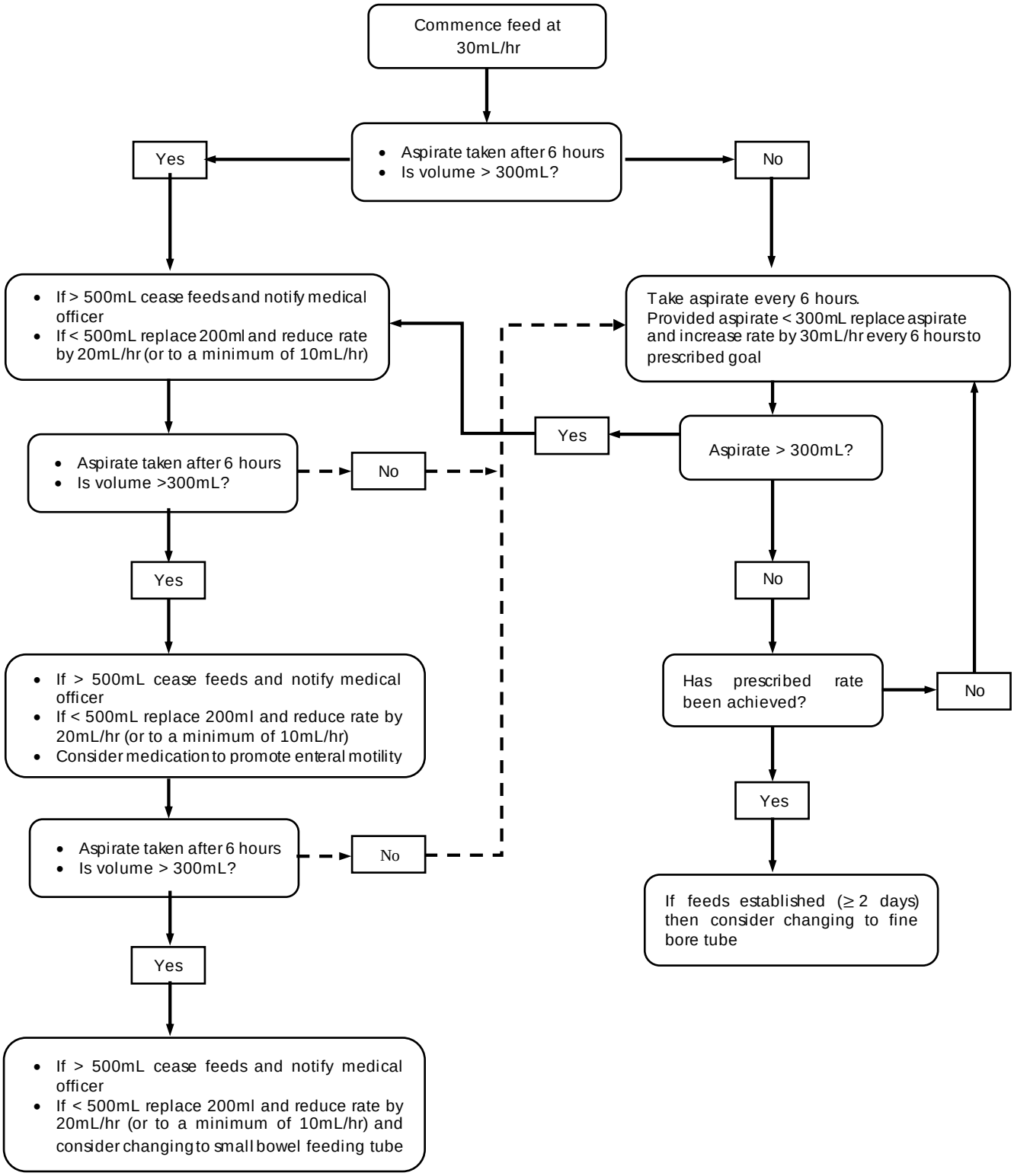
Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
				feedback, 2) Evidence-based educational outreach visit; 3) Site-specific interventions to overcome identified barriers; 4) performance coaching; 5) Local ICU opinion leaders to influence attitudes and behaviour change; 6) Network meeting		
Heyland, D., Stephens, K.E., Day, A. G. & McClave, S.A. (2011). The success of enteral nutrition and ICU-acquired infections: A multicentre observational study	Prospective obersvational study	207 patients from 3-tertiary medical and surgical ICUs Inclusion >18 years Excluded: elective surgical patients, overdoses, patients expected to stay <24hours in ICU Within the secondary analysis, patients who were mechanically ventilated >72 hours, received EN prior to ICU and receiving PN were excluded.	Level III	Aim: evaluate the relationship between increasing success with enteral nutrition and acquired infection in the ICU Included 3-tertiary medical and surgical ICUs No attempt of clinical practice standardisation was made across the participating ICUs The general practice guiding EN management included: EN provided within 24-48 hours, feeds increased to goal hourly rate dependent on EN tolerance, GRVs checked every 4 hours, if GRVs less than 200-250ml – feeding rate increased or continued at goal rate, goal rates determined by dietitian using standard formulae. If persistent high GRVs/aspirates were to occur, prokinetics were administered or eventually a small bowel feeding tube. PN was prescribed by clinical team as indicated. Arterial or venous blood glucose levels were assessed daily in the morning and frequently throughout the day. Dose of insulin was prescribed by glycemic control protocol – blood sugar levels were titrated between 4.0 – 9.0 mmol/L Clinical outcomes measured Ventilator-free days in 28 days; ICU LOS, and 28-day mortality Diagnosis of ICU-acquired infection defined as infection presented after 72hr admission. Suspected infection defined by	Nutritional Adequacy Average energy and protein prescription by the ICU dietitian was 23kcal/kg/day and 1.0g/kg protein Mean adequacy of calories and protein meeting prescribed requirements was 48.9% (range: 0-120%) and 45.0% (range: 0-120%) respectively. Clinical outcomes Patients remained ventilated for 9.1 days (IQR: 6-11 days), in ICU for 13.5 days (IQR: 7-14) and 25.1% and 21.7% developed an infection after 72 and 96hrs respectively. Common infections after 72h included pneumonia (12%), catheter related infections (7%), urinary tract symptomatic infection (3%) and catheter related primary bactremia infection (3%). 28-day overall mortality was 29% Relationship between EN and clinical outcomes greater amounts of energy and protein were consistently associated with a reduction in infection but only achieved levels near statistical significance when considering the risk of at least 1 probable infection after >96 h (OR: 0.32, 95% CI: 0.10-1.02, p=0.054 and OR: 0.40, 95% CI: 0.18-0.89, p=0.024 per 1000 kcal/day of energy and 30 g/day of protein, respectively). Trend towards lower pneumonia infections developed after 96h with patients receiving greater amounts of energy (OR: 0.4, 95% CI: 0.10-1.53, p=0.18) and protein (OR: 0.42, 95%CI: 0.16-1.09, p=0.075) Greater amounts of energy and protein were not significantly associated with mortality (OR: 0.99, 95%CI: 0.48-1.98, p=0.97 and OR: 1.01, 95%CI: 0.62-1.63, p=0.98) or or ventilator-free days (– 1.16, 95%CI: 4.01 – 1.68, p=0.42 and -0.72, 95%CI: 2.66-1.22, p=0.47).	Increased energy intake to prescribed requirements may reduce the likelihood of infections. Although, as conducted as a prospective study, unable to conclusively draw that association.

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
				presence of new positive culture result or initiating new antibiotic after 72hrs 'Probable' and 'Possible' definitions were given for each type of infection to reflect degree of probability and standardisation of definition.		
Sajid et al. (2014). An integrated systematic review and meta-analysis of published randomized controlled trials evaluating nasogastric against postpyloris (nasoduodenal and nasojejunal) feeding in critically ill patients admitted in intensive care unit	Systematic review: meta-analysis	Twenty RCTs included in analysis Total 1496 patients (760 NG feeding group and 736 post-pyloric feeding group)	Level-I adequate power calculation; allocation concealment; intention-to-treat analysis Blinding was not adequate No clear description for methodological quality of included trials were assessed – used two published guidelines to assess quality and GradePro tool	Aim: to systematically analyse the RCTs comparing effectiveness of NG vs post-pyloric (PP) feeding in critically ill patients of various medical and surgical disciplines admitted into Intensive Therapy Unit Inclusion criteria: (1) RCT; (2) comparison between NG feeding and PP feeding, (3) evaluation of aspiration pneumonia and/or ventilation pneumonia rate, adequate caloric intake, tube displacement rate on both intubated and non-intubated patients; (4) main outcomes preferable reported on intention-to-treat analysis; and (5) trials in surgical and intensive care patients requiring nutritional support Primary outcomes: aspiration pneumonia (ventilator associated pneumonia or nocosomial pneumonia) Secondary outcomes: incidence of high gastric residual volumes, mortality, ITU LOS, reduced caloric delivery and gastrointestinal complications (nausea, vomiting, diarrhoea, abdominal distention, reflux and gastrointestinal bleed).	Primary outcome (Aspiration pneumonia) A significant risk reduction for aspiration pneumonia incidence for patients fed post-pyloric (OR = 1.41; 95%CI: 1.01-1.98; z=2.03; *P* = <0.04) – no heterogeneity among the seven studies that reported aspiration pneumonia (t2=0.05, X^2test=16.73, df=15, P=0.34; I^2=*10*%) Secondary outcomes There was no significant difference between NG and PP fed groups for the risk of gastrointestinal complications (nausea, vomiting, diarrhoea, abdominal distention, reflux and gastrointestinal bleed). Included 13 trials – high heterogeneity between groups No significant difference in the 16 trials that reported overall mortality (OR=0.86; 95% C= 0.64-1.15; z=1.02; P=0.31) Gastric residual volumes (GRV) were significantly higher in the NG feeding group – may be attributed to higher heterogeneity between groups (3.95; 95% CI, 1.19 – 13.14; z=2.24; P=0.03;) Analysis based on GRV >300-500ml of seven trials Significant heterogeneity (t2=1.78, X2-test=22.78, df=6, P <0.001; I2=73%) No significant difference between NG and PP feeding groups for ITU length of stay The NG feeding group was associated with lower delivery of calories compared to the PP fed group (standardized mean difference = -1.02; 95% CI=-1.73 - -0.31; z=2.82; P<0.005) Significant heterogeneity (t2=1.22, X2-test=173.03, df=9, P<0.00009; I2.95%)	Aspiration pneumonia incidence is reduced when fed post-pyloric No significant differences with GI complications, mortality, High heterogeneity in groups may be reflected by patient types, conditions, use of standard protocols
Dean Adam et al. (2013). Comparisons between intragastric and small intestinal delivery of enteral nutrition in the	Systematic Review and meta-analysis	1178 patients from 15 Level-II RCTs >18 years admitted into ICU	LEVEL I None of the included RCTs involved blinding	Aim: to compare incidence of ICU-acquired pneumonia and other patient clinical-related outcomes in small-bowel and intragastric EN fed critically ill patients.	Primary outcome – pneumonia The incidence of ICU-acquired pneumonia in small bowel fed patients compared to gastric tube fed patients was associated with a reduced relative risk (RR: small bowel vs gastric: 0.75, 95%CI: 0.60 – 0.93, *P*=0.01, I^2 = 11%). Following adjusting for confounding trials the	Pneumonia incidence is reduced through post-pyloric feeding Nutritional delivery according to requirements remains not different.

Citation	Study design & Setting	Participants	Study quality	Intervention aim & description OR Indicator/Issue of interest	Outcomes	Comments
critically ill: a systematic review and meta-analysis				Primary outcome: ICU-acquired pneumonia Secondary outcome: mechanical ventilation duration; ICU and hospital LOS, mortality and nutritional intake Subgroups: Studies that used microbiological data to evaluate incidence of pneumonia.	association was still significant (RR: 0.75 (0.56 to 1.00); *P*= 0.05; I^2 = 21%). This remained significant following subgroup analysis for studies that included microbiological diagnosis of ICU-acquired pneumonia (RR: 0.72 (0.55 to 0.93); *P*= 0.01; I^2= 0%). Secondary Outcomes No significant difference in the relative risk for ICU and hospital LOS; duration of mechanical ventilation and mortality, even following adjusting for confounding trials there was no difference. Unable to identify a significant difference in nutritional administration between small bowel and gastric tube fed patients. There was high variation in the methods of this measurement taken among the trials that reported nutrition delivery.	

Appendix C. ICU EN Feeding Protocol

Figure 1. ICU Enteral Nutrition Feeding Protocol



Appendix D. Author Guidelines

JPEN author submission guidelines PDF can be obtained from the url below.

http://www.nutritioncare.org/Publications/JPEN_Author_Instructions/

Appendix E. ENCIP cover letter

15th August 2016

Dear Dr. Brophy and Ms. Petersen,

Re: Enteral Nutrition in Critically Ill Patients: The ENCIP Study

I would like to submit a protocol for consideration of ethical exemption based on the nature of the study. The proposed audit will be carried out in Mater Health Intensive Care Units. There are no interventional components to this study. It is an observational audit of routine clinical practice which will be used to assess adherence to standard nutrition protocols as well as analyse its subsequent effect on patient clinical outcome markers. The key aims of the audit are to determine: 1) The adequacy of enteral nutrition provision compared to estimated energy and protein requirements, 2) Factors associated with meeting energy and protein requirements, 2) Factors associated with meeting energy and protein requirements; and 3) Patient health-related outcomes associated with meeting energy and protein requirements.

Data obtained from this audit will be used to inform implementation of strategies designed to improve nutrition provision to critically ill patients in the ICU if required. Outcomes of this audit will likely be presented at local and national conferences as well as be published in a peer-reviewed journal.

I have included the following documentation to assist you in reaching a decision. These include:

1. Study Protocol, titled: "Enteral Nutrition in Critically Ill Patients: The ENCIP Study", Version 1, Date 15/08/2016
2. Case report form, version 1, Date 15/08/2016
3. Curriculum Vitae (CV) for Dwayne Garcia
4. Mater ICU enteral feeding order form which will provide insight on standard clinical practice

Mr. Garcia will be closely supervised by senior clinician researchers on-site (myself, Ms. Tolcher and Dr. van der Meij) as well as at university (Dr. Marshall) for the entirety of this project.

On behalf of the investigating team I would like to thank you for taking the time to consider this application. Please contact either Debbie Tolcher or myself on pager number 0350 should you have any further enquiries regarding this submission. I look forward to hearing from you.

Kind regards

Ra'eesa Doola
Accredited Practising Dietitian, Mater Health Services

Appendix F. Research Protocol

Enteral Nutrition in Critically Ill Patients: The ENCIP Study

Dwayne Garcia[1,2], Ra'eesa Doola[3,4], Debbie Tolcher[3,5], David Sturgess[3,6], Skye Marshall[1,7] Barbara van der Meij[1,3,8]

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PROJECT SYNOPSIS

Underfeeding patients in a critically ill state has various adverse effects including, but not limited to, a loss in lean body mass, poor wound healing, increased risk of infection, organ dysfunction, weakened respiratory muscles and subsequent increased duration of mechanical ventilation and overall increased morbidity and mortality.[1-3] Mater Health Services (MHS) have an established protocol titled: "Enteral Feeding Order and Flowchart – ICU" which guides enteral nutrition delivery in critically ill patients admitted to the Mater Hospital Brisbane (MHB) and the Mater Private Hospital (MPH) intensive care units (ICUs). In adults receiving enteral nutrition admitted to two ICUs in Queensland, Australia, this audit aims to determine:

1) The adequacy of enteral nutrition provision compared to estimated energy and protein requirements,
2) Factors associated with meeting energy and protein requirements; and
3) Patient health-related outcomes associated with meeting energy and protein requirements.

1.0 BACKGROUND

Underfeeding patients in a critically ill state has various adverse effects including, but not limited to, a loss in lean body mass, poor wound healing, increased risk of infection, organ dysfunction, weakened respiratory muscles and subsequent increased duration of mechanical ventilation and overall increased morbidity and mortality.[1-3] In a large international study (33 countries, n=7,872 participants) it was found that patients who received at least two thirds of their energy requirements were 36% less likely to die than those who received less than one third of their requirements (OR 0.67; 95% CI 0.56-0.79; $p < .0001$).[2]

While it is widely recognised that nutrition is an integral therapeutic component of care in the ICU, there is a high prevalence of underfeeding critically ill patients worldwide.[2 4] The International Nutrition Survey (INS) found that the average energy and protein delivered was approximately 60% of prescribed requirements. This is substantially lower than the minimum of 80% shown to be associated with a reduction in mortality.[2 4 5] The INS initially evaluated whether local, national and international sites were implementing its evidence based guidelines.[6]

Ranking scores are given for each participating ICU based on their performance, where 1 is ranked the highest. Two participating units in Queensland, Australia, were at Mater Health Services (MHS), who participated in the 2008 and 2011 surveys. The MHS ranks based on the audit for 2011 were 34 and 35 (Mater Hospital Brisbane and Mater Private Hospital respectively) out of the (total number) Australian ICU sites and 136 and 137 out of the 183 worldwide. This indicated that MHS had a number of areas to work on to improve rates of underfeeding.

Through liaison with key stakeholders, reasons for underfeeding were identified and strategies to improve these barriers were formulated and implemented. This occurred through wide collaboration with intensivists, nursing staff, pharmacy, dietitians and management, resulting in a new enteral nutrition formula being introduced and an updated enteral feeding protocol being implemented. However, it has not yet been evaluated. This audit will examine the impact of this new protocol to establish 1) the adequacy of nutrition support in enterally-fed adults admitted to the two MHS ICUs, 2) explore reasons patients were unable to meet recommended nutrition targets during their admission, and 3) determine the patient health-related outcomes related to feeding.

1.1 Research Aim

In adults receiving enteral nutrition admitted to two ICUs in Queensland, Australia, this study aims to determine:

4) The adequacy of enteral nutrition provision compared to estimated energy and protein requirements,
5) Factors associated with meeting energy and protein requirements; and
6) Patient health-related outcomes associated with meeting energy and protein requirements.

2.0 METHODS

2.1 Study Design

This study is an audit of clinical practice from September 2016 to March 2017

2.2 Study Sample

This study will be a single-centre study conducted within the Intensive Care Unit, Mater Hospital Brisbane (MHB) and in the Intensive Care Unit, Mater Private Hospital Brisbane (MPH). There are 16 and 10 ICU beds in the MHB and MPH respectively.

Adult inpatients (≥18 years) will be consecutively sampled from MHB and MPH ICU sites, with a placement of a nasogastric tube (NGT), nasojejunal tube (NJT), orogastic tube (OGT), orojejunal tube (OJT), percutaneous endoscopic gastronomy (PEG) or jejunostomy tube for the primary purpose of providing EN during the first 7 days of ICU admission. Patients not receiving EN or receive mixed route of nutrition support (i.e. EN and parenteral nutrition or EN and oral) will be excluded from this audit.

The anticipated sample size will be 40 patients, incorporating 20 patients each from both MHB and MPH, reflecting expected patient numbers throughout the investigation period of October 2016 until February 2017. All eligible patients will be sampled consecutively. Eligible patients will be identified through admission notes, ward bed lists (using Trendcare), ICU bed charts and medical charts.

As an observational audit of routine clinical practice, with no intervention, the patient will not be required to take part in any study procedures or specific data collection.

2.3 Data collection

Participant characteristics will be recorded at baseline and will include age, gender, reason for admission, weight on admission, height, need for mechanical ventilation, oedema (if recorded in medical notes).

The data collection period will be from October 2016 until February 2017. Baseline will be considered the day of admission or the day of EN commencement, and outcome variables will be collected from daily records for the duration that the patient receives EN or is separated from the ICU, unless specified otherwise. Participants discharged to another ward in Mater Health Services will have continuing weekly data collection (for patient health-related outcomes) until hospital separation.

Data will be collected via review of medical notes, with confirmation sought from ICU staff where necessary.

2.4 Outcomes

To assess *Aim 1: The adequacy of enteral nutrition provision compared to estimated energy and protein requirements*, the following variables will be captured:

1. Adequacy of nutrition provision, which will be considered the percent of energy and protein estimated requirements met during the enteral feeding period.

The adequacy of nutrition provision is defined by meeting both criteria 1 and 2 below:

1. ≥80% estimated energy requirements (EER) met for all days of enteral feeding in the ICU excluding the day of intubation and extubation (Y/N)
2. ≥80% estimated protein requirements (EPR) met for all days of enteral feeding in the ICU excluding the day of intubation and extubation (Y/N)

The percent EER and EPR met will be calculated as the amount of energy or protein from EN received divided by EER or EPR x 100. Estimated energy and protein requirements will be calculated using the minimum value in the range provided by weight-based equations (105 kJ/kg/day from the 105-125 kJ/kg/day range and 1.2 g/kg/day from the 1.2-2.0 g/kg/day range)[4,5] or indirect calorimetry.

To assess *Aim 2: Factors associated with meeting energy and protein requirements*, an exploration of factors associated with meeting energy and protein requirements will be informed by the investigation of adherence to the current enteral feeding protocol "Enteral Feeding Order and Flowchart – ICU".

In order to evaluate how the "Enteral Feeding Order and Flowchart – ICU" protocol is implemented and which components may impact most strongly upon nutrition adequacy, the protocol was considered to have five domains which were used to generate the variables to assess were informed by existing literature[7,8], implementation of the enteral feeding protocol and clinician experience: Monitoring, Adjustment, Prescription, Referral and Medication.

1. Proportion of patients commenced on EN within 24-48 hours of ICU admission unless clinically contraindicated

2. Appropriate EN prescription (Y/N). Determined by:
    - appropriate goal rate prescribed upon initial EN commencement, initial feeds commenced at 30mL/hr, appropriate 1.5kcal/ml EN feeding formula prescribed

3. Appropriate EN monitoring (Y/N). Determined by:
    - checked aspirates every 6 hours, achieving prescribed rate

4. Appropriate EN adjustment (Y/N). Determined by:
    - starting rate increased 30mL/hr when indicated, reduce rate by 20mL if aspirate between 300-500ml, rate adjusted for appropriate reason, referrals made to medical officer or allied health professional when indicated

5. Appropriate medication use (Y/N). Determined by:
    - prokinetic used when aspirates between 300-500mL, appropriate dose and frequency of prokinetics

Further exploratory variables, which may be associated with meeting nutrition requirements include:

6. Time of fasting prior to extubation: hours
7. Severity of illness: illness score
8. Temporary EN cessation: Y/N, duration of cessation
9. Hypergylcaemia: number of occasions of BGL ≥11.1mmol/L; percent days with at least one episode of BGL ≥11.1mmol/L
10. Steroid administration: Y/N, reason administered
    - Bowel protocol being followed by staff: Y/N determined by monitoring bowel movements, adjustment of medications, delivery of indicated medications
11. Correct patient placement: Y/N, determined by head of bed: 30/45º

To assess *Aim 3: Patient health-related outcomes associated with meeting energy and protein requirements,* clinical outcomes were chosen which may be impacted by adequate nutrition provision. The following outcomes will be collected on all patients audited:

1. ICU length of stay (LOS; days excluding day of admission

2. total hospital length of stay (days excluding the day of admission),
3. discharge location (pre-existing residents/other),
4. mortality in ICU (Y/N), mortality in other acute care wards (Y/N).

2.5 Data Management

Data will be managed in accordance with the Australian Code for the Responsible Conduct of Research. All participants will be allocated a participant number which is re-identifiable to the researchers during the study period. Identifiable information will be used to link participant's medical record numbers and their participant number, and will be recorded on one hardcopy form which will remain in a locked drawer within the Nutrition & Dietetic Department of Mater Health Services. Upon conclusion of the data collection period, the hardcopy participant information form will be recorded on an Excel spreadsheet which will be password locked. Three named investigators (DG, RD, BVDM) will retain this locked spreadsheet for a period of 5 years after the date of research publication, after which point it will be permanently deleted. Upon conclusion of the data collection period, the hardcopy of the participant information form will be shredded.

All other forms (participant baseline characteristics form and participant outcome data collection form) will be de-identified hardcopies used in the ICU for data collection. Electronic data will be kept for a period of 15 years, for further use in benchmarking and quality assurance purposes by Mater Health Services. Re-identifiable hardcopies of all data collection forms will be held in a locked drawer in the Nutrition & Dietetic Department of Mater Health Services for a period of 15 years after the research is published, and then shredded.

3 . 0 DATA ANALYSIS

All statistical analysis will be completed using SPSS version 22.0 [2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.]. Statistically significant results will be considered at p-values <0.05 and/or 95% CI which does not include the no effect value (0 for a rate/proportion or 1 for a ratio). Descriptive statistics will be used to characterise the participant

descriptors and to report all outcome measures of the sample population (mean ± SD/SE for normal variables, median (inter-quartile range) for skewed variables, 95% CI; or proportions and percent) for the total group and per ICU site. Normality will be assessed using the Shapiro-Wilk test and homogeneity of variance will be assessed using Levene's test for all continuous variables.

In order to address the second aim, "≥80% estimated energy requirements (EER) met for all days of enteral feeding in the ICU excluding the day of intubation and extubation (Y/N)" will be used to group participants as "met nutritional requirements" and "did not meet nutritional requirements". This categorical variable will be used as an "outcome variable", from which all potential factors associated with not meeting the nutrition requirements (section 2.6.1) will be considered explanatory variables. Association between these explanatory variables and the outcome variable will be tested for association using independent *t*-tests for continuous variables (and Mann-Whitney *U* tests for non-parametric variables) and chi-square tests for categorical variables.

In order to answer the third aim, the "met nutrition requirements" and "did not meet nutrition requirement" groups will be considered as an explanatory variable for the secondary outcome variables that reflect patient health-related outcomes. Association between the explanatory variable and the outcome variables will be tested using linear regression. Generalised linear models will be created to identify variables that best predict clinical outcomes and account for potential counting variables (where relevant)

5.0 REFERENCES

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4. Heyland DK, Dhaliwal R, Wang M, et al. The prevalence of iatrogenic underfeeding in the nutritionally 'at-risk' critically ill patient: Results of an international, multicenter, prospective study. Clinical Nutrition 2015;**34**(4):659-66.
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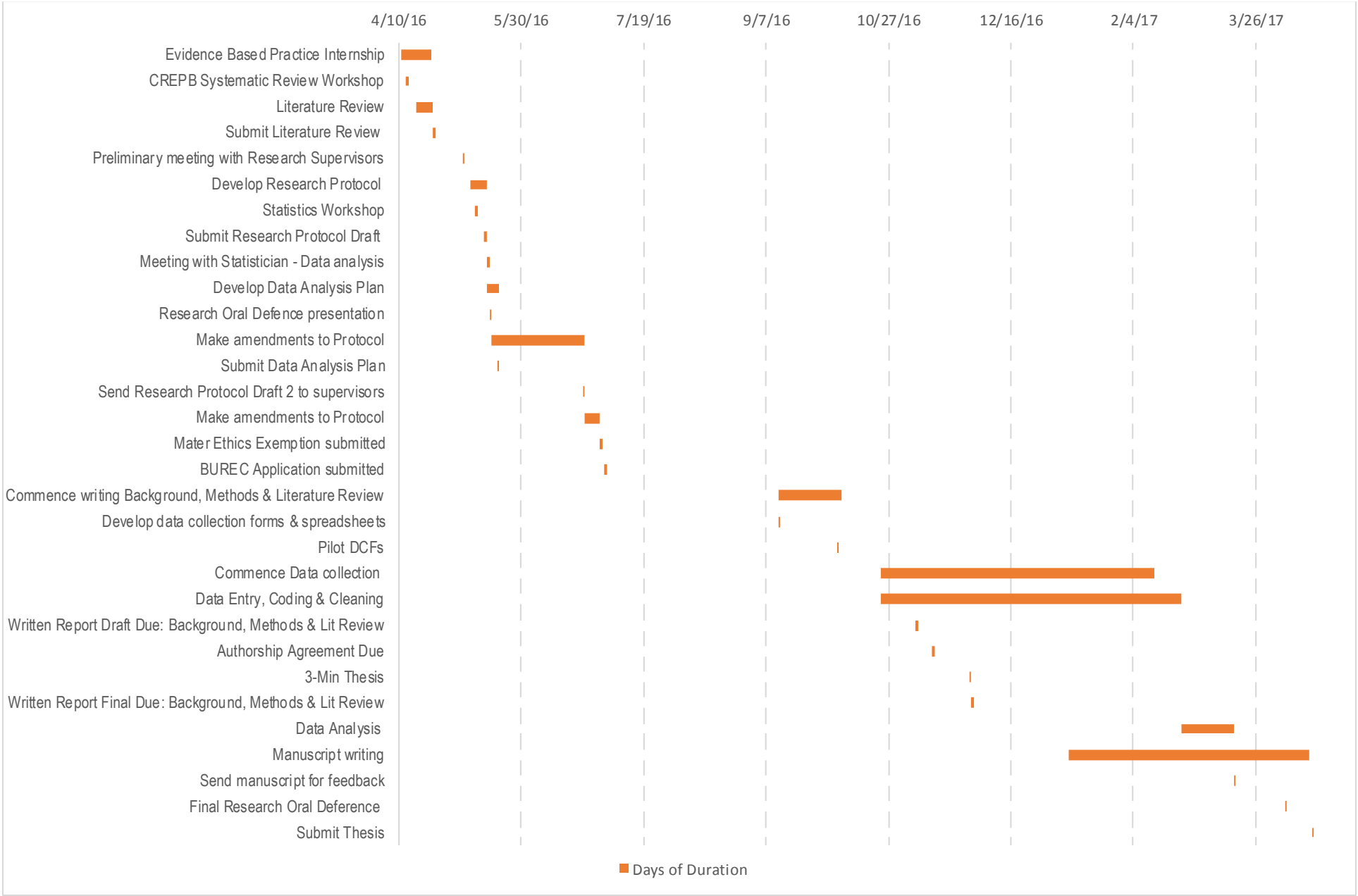
Appendix G. ENCIP Gantt Chart



Appendix H. Data Collection Forms

Patient demographics Sticker

Study ID #: MBH / MPH_____

Age: Gender: ☐ M ☐ F

ADMISSION AND MEDICAL INFO	
Admission to hospital date:	Admission to ICU date:
Admission Reason:	Comorbidities:
HOB elevated ☐ Y ☐ N	
Presence of oedema if documented: (incl date):	APACHE III
VENTILATION Intubation: ☐ Y ☐ N Date: Time: Extubated: ☐ Y ☐ N Date: Time: Re-intubated: ☐ Y ☐ N Date: Time:	
Discharge from ICU date	Discharge from hospital date

Anthropometry and EER/EPR

Weight:	Ht:	BMI:	Adj IBW:
EER			
EPR			
Goal rate (as per dietitian):			
Mode of EN:			

Study ID_____ STUDY DAY _____ Date_____

Commenced at 30mL/hr ☐ Y/ ☐N ☐Intubated ☐Mortality

EN PROVISION

Product @ Rate (x/24)	0100	0200	0300	0400	0500	0600	0700	0800	0900	1000	1100	1200	1300	1400	1500	1600	1700	1800	1900	2000	2100	2200	2300	2400

Reason for Adjustment			
Appropriate Adj	☐ Appropriate Increase	☐ Appropriate Decrease	☐ Appropriate referral to MO
% EER over the day		>80% EER	☐ Y/ ☐N
% EPR over the day		>80% EPR	☐ Y/ ☐N
EN Cease	☐ Y / ☐ N Time Period:	Reason:	

ASPIRATES

Time	Asp Vol	>300	>500	EN Adjusted?	Rate Change	Prokinetics: Y/N (type, dose, freq)	Vol Discarded	Vol Returned

Propofol & Total of day	Propofol given >6hrs ☐ Y ☐ N Total (mL) over day:
Bowel Protocol Followed	D___ of EN, D___ of protocol ☐BO ☐BNO Appropriate daily regime: ☐ Y ☐ N

Daily BGL

Time	0100	0200	0300	0400	0500	0600	0700	0800	0900	1000	1100	1200	1300	1400	1500	1600	1700	1800	1900	2000	2100	2200	2300	2400
BGL																								
Insulin units																								

Steroids o Cortisone o Dexamethasone o Hydrocortisone o Methylprednisone o Frudrocortisone	Date started: Dosage: Are they still on steroids? ☐ Y ☐ N Date finished:
Complications	
Appropriate referral	Reason for referral: